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REVIEW Article

Bulk and Single-Cell Epigenomics Analyses using Deep Learning Frameworks

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ABSTRACT

Epigenomics studies sit at the forefront of omics research. As a building block of the current knowledge on the intricate gene regulatory networks, epigenetic regulation uncovers the complexity that underlies modifications affecting gene expression without having any impact on the actual DNA sequence. Several advanced features have been demonstrated by epigenetic studies- DNA methylation, chromatin accessibility and organization, histone modifications, all contributing to a larger scale landscape that comprises higher order, often non-linear relationships between its elements. Continuous technological improvement forged a strong link between bioinformatics and omics while searching for the necessary means to investigate such complex connections. Thus, gaps previously left by the lack of suitable computational tools have been filled by artificial intelligence lately. Delving deeper into the epigenetic network, the paradigm has progressively shifted towards single-cell focused studies that promised to solve the issues regarding heterogeneous tissues. This accelerated pace of innovation propels the simultaneous development of sequencing methods that support epigenomics studies and of computational tools encompassing deep learning frameworks and quantum resources designed to perform epigenomics-related prediction tasks. Future directions of research are guided by the optimistic perspective of highly performant technological means that will drastically reduce technical noise, eliminate negative interferences, including data sparsity, batch or dropout effects, enabling an unprecedented quality of omic predictions.

Keywords

Epigenomics, deep learning, DNA methylation, chromatin accessibility, histone modification, bulk sequencing, single-cell sequencing.

Abbreviations

Artificial intelligence (AI); deep learning (DL); 6-methyladenosine (6mA); 5-methylcytosine (5mC); micro ribonucleic acid (miRNA); transcription factor (TF).

SUMMARY

1. Introduction

Recent advancement in omics research has empowered scientists to perform higher accuracy genetic testing and to increase accessibility. Various methods have been employed to enhance multiomic analysis. Gene expression studies have seen the benefits emerging from the refined genomic, transcriptomic, epigenomic and even proteomic investigations. While genomics look at the precise nucleotide sequence and track the influence that mutations inflict upon different cellular processes, including transcription and further translation into proteins which gives a certain phenotype, epigenetic modifications refer to changes that do not affect the DNA sequence per se, but they produce reorganization in the chromatin packaging, having consecutive effects on the steps of the central dogma of molecular biology[1]. Epigenomics explore the complete set of changes that reflect onto the gene activity, but do not alter the nucleotide succession within the gene. Thus, modifications such as DNA methylation, histone modifications, chromatin spatial organization, non-coding RNA or sites for transcription factor binding can switch gene expression between on and off states. Gene expression is a strictly controlled process that receives regulatory signals from these multiple epigenomic layers. Epigenetic profiles can provide insight into disease phenotypes (such as cancer, for example) whenever the cell is subjected to stress factors that might produce shifts in the direction of differentiation, serving as a proof for how environment by itself impacts health and the fate of cells having the same genetic information, but different developmental trajectories[2]. Diversification of the sequencing information portofolio has nonetheless improved the understanding of the processes underlying gene regulatory networks, but has also raised the issue of data complexity. Such problems uncover two central directions of seeking solutions- one focuses on increasing the resolution of the analysis through upgrading from bulk to single-cell sequencing[3], while the other tries to deal with the high-dimensionality of the datasets and find suitable computational approaches that simplify the workload through artificial intelligence resources[4]. Deep learning models have been designed to answer the call for improvement of the epigenomic studies in terms of accuracy and time efficiency, finding extensive applications for DNA methylation analysis[5], predicting chromatin interactions[6] and also various other layers such as histone modifications, miRNAs or long non-coding RNAs[2]. This review aims to offer a brief overview of the main modalities of integrating deep learning (DL) frameworks into epigenomic research projects, marking the transition towards the single-cell centered studies that require higher technological resources. Additionally, it approaches the recent emergence of quantum computing in biology applications as a topic that promises to enhance the quality of epigenomic analysis in the near future.

2. Deep Learning Models Crossing the Epigenomics Layers

Epigenetics covers mechanisms that enable cells to switch gene expression on and off while preserving the nearly constant genome. This behaviour allows the existence of multiple functional and stable cellular states depending only on reversible modifications identified as epigenetic marks, ranging from the addition of chemical tags like DNA methylation or acetylation or likewise histone modifications to complex 3D chromatin organization and accessibility for the transcriptional machinery[7] (see **Figure 1** for a summary of the main epigenetic mechanisms discussed in this section).

2.1. DNA methylation

Epigenetic analysis accounts for multiple modifications that interfere with the downstream cellular processes. DNA methylation is one of the best studied phenomena that contribute to the epigenomic landscape. Methylations such as 5-methylcytosine (5mC) and 6-methyladenine (6mA) play important roles in various biological processes. Sequencing methods employed for the study of DNA methylation vary between using short-read and long-read sequencing like Nanopore that are able to distinguish signals originating from modified nucleotides. Computational resources to suit the interpretation of the sequencing datasets have been developed. Ni et al. introduced a DL framework named DeepSignal[8] to enhance the prediction of DNA methylation states directly from Nanopore sequencing reads. An application for Nanopore reads has also been developed by Stanojević et al, their model, Rockfish[9], performing precise 5mC predictions. Other works have approached the CpG islands methylation through the means of Illumina sequencing reads, building DL models like

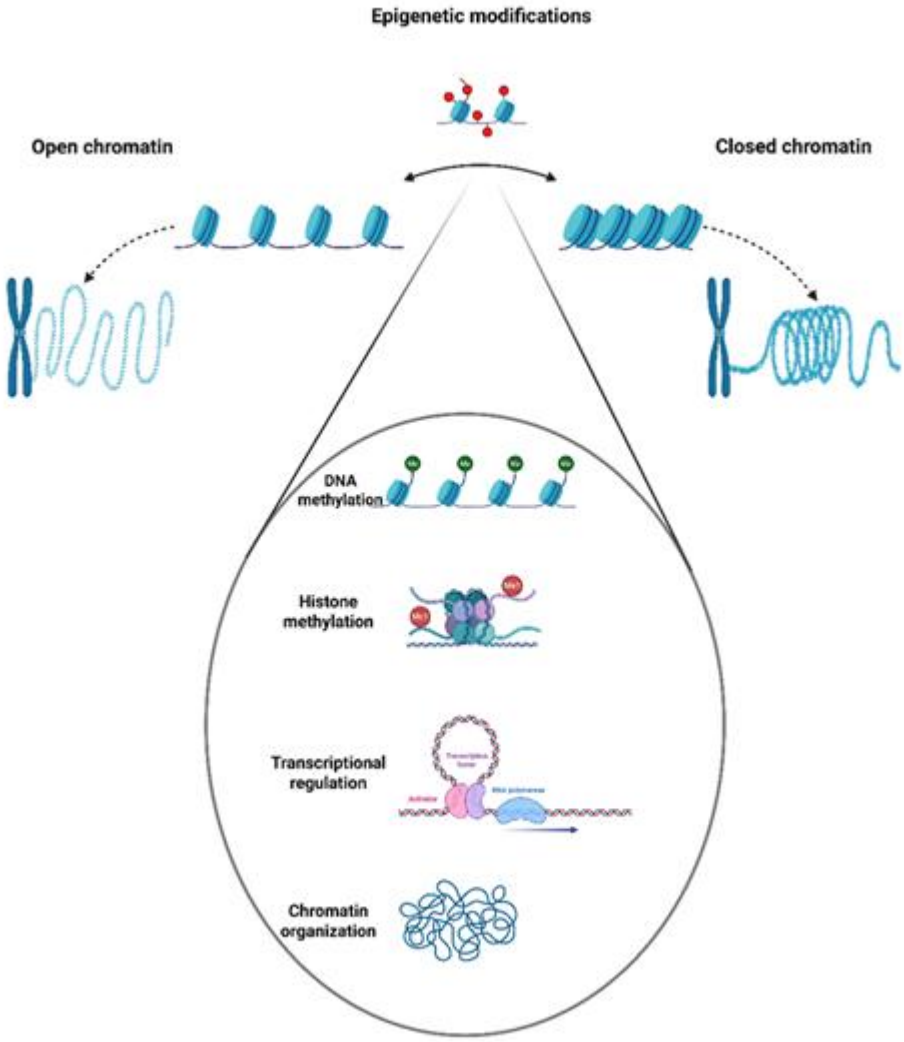

Figure 1. Summarizing diagram comprising the main epigenetic traits presented.
The figure shows the reversibility of epigenetic modifications, allowing the interchange between open and closed chromatin states depending on the regulatory signals. In the lower half of the figure- the main epigenetic marks described in Section 2. Created in BioRender. Palastea, E. https://BioRender.com/bsjlvv0

MethylNet[10] that performs well in terms of predictive tasks starting from DNA methylation states. Studies involving the combined use of DL and methylation information have shown potential as tools for disease detection, particularly cancers (cfMethylPre[11] for circulating cell-free DNA methylation profiles and MSI-XGNN[12] for leveraging microsatellite instability based on methylation and transcription biomarkers). These methods are applied to bulk sequencing data, thus lacking a correct representation of the heterogeneity of the cell population. Treating all CpG islands as if they are identical fails to give a good correlation between gene expression and methylation status. This issue has been pointed out by Xu et al., who developed a model called CHALM[13]; their solution infers that each bisulfite sequencing read corresponds to a single cell from the bulk sequencing dataset[13].

Refining the quality of predictions required an increased resolution of the sequencing data used both for training and for testing the computational models. Moving towards single-cell modalities helps with

capturing a more detailed landscape of the methylation status, but also requires more advanced frameworks to deal with the highly dimensional data. Scientists keep up with the new technology, developing new DL models that can extract the patterns from single-cell sequencing reads. A few relevant examples are a model built by Li et al., based on DL and explainable AI (XAI) that infers predictions regarding aging from single-cell and epigenetic data[14]; MAgeNet[15], another framework that performs on single-cell data for DNA methylation information and predicts chronological age; scMeFormer[16], a platform that uses methylation and single-cell data to identify epigenetic modifications that occur in schizophrenia; GraphCpG[17] and MambaCpG[18], DL methods that work on imputation of single-cell methylomes.

Therefore, a full depiction of the DNA methylation phenomenon can be inferred only when details are gathered from both bulk and single-cell datasets, each of the methods contributing in a distinct way, and the same synergistic effect can be attained when these two sequencing technologies are applied for investigating other epigenetic layers, including chromatin organization and histone marks.

2.2. Chromatin accessibility

Chromatin accessibility translates to the permissibility of the DNA duplex for other macromolecules to attach. This central epigenetic property allows molecules such as transcription factors (TFs), enhancers, promoters to bind to certain genomic sequences and influence downstream processes. The complex gene regulatory networks initiated by these elements have also requested the integration of advanced technology that can leverage the non-linear relationships that often occur. Models like DeFine deal with the quantification of TF- DNA binding intensities and simultaneously enable the evaluation of functional non-coding variants[19], while CoRE-ATAC[20] is capable of classifying regulatory elements based on both single-cell and bulk sequencing data. Noteworthy, Luo et al. created DECA[21], a framework that captures chromatin accessibility profiles from bulk and single-cell ATAC-seq[22].

A few frameworks focus solely on characterizing chromatin organization and accessibility from bulk sequencing reads. For example, DeCOOC[23] deconvolutes high-throughput chromosome conformation captured from bulk data obtained from adipose tissues, and Cellformer[24] uses bulk ATAC-seq to leverage epigenetic signatures that appear in Alzheimer's disease.

On the other hand, certain models perform the analysis of single-cell datasets for inferring TF binding predictions (REUNION[25]), cell-type annotation (scAttG[26]), cis-regulatory elements localization for single-cell epigenetic data (scEpiLock[27]).

2.3. Histone modifications

Histone modifications have a major impact on chromatin packaging and subsequent processes in gene expression regulation. Besides DNA methylation, various chemical reactions take place at the level of histones. Histones undergo changes such as methylation, lactylation or crotonylation[28,29]; these epigenetic traits contribute a significant proportion to the spatial conformation of DNA, determining either closed or open chromatin states that later reflect onto the levels of gene expression. Open chromatin regions are permissive to transcription and can recruit TFs, leading to active gene expression, while closed chromatin silences the domain due to the restricted access of transcriptional proteins[28]. Among the epigenetic biomarkers, there is an important number of histone modifications that can be identified. Advancement in bioinformatics research has also propelled the creation of DL models to identify these histone marks and investigate their significance. A range of AI-powered studies have a detailed perspective on lactylation, such as the hybrid deep learning platform proposed by Zhang et al. who linked lactylation to resistance to treatment in ovarian cancer and pointed these histone modifications as potential therapeutic targets[30], or a more traditional machine learning Seurat[31] setup used by Chen et al. to characterize lactylation in acute myeloid leukemia in single-cell data[32]. Another histone mark, lysine crotonylation, occurs in both histone and non-histone proteins. Lysine crotonylation can be evaluated using the DeepMM-Kcr[33] DL model that predicts these post-translational modifications that seems to play an important role in gene expression and chromatin structure, being associated with active transcription. Applied for a different epigenomic task, a framework named COCOA[34] has been employed for leveraging chromatin organization profiles based on histone marks, thus extracting important 3D epigenomic architectural aspects of chromatin compartimentalization.\

3. Challenges and Future Perspectives

The emergence of recent technologies has marked the transition towards precision medicine. The shift from traditional statistical methods to AI-enhanced platforms accelerated the rate of uncovering new patterns and mechanisms underlying gene regulation. A new paradigm arised as single-cell studies have been widely adopted as a way of dissecting heterogeneity within a tissue. Thus, one major aspect of traditional bulk sequencing that previously hindered scientists from observing more than an average of the aggregated data has been overcome. Bulk sequencing offers a more convenient alternative in terms of time and resources, but has an intrinsic limitation stemming from its lack of representation of rare cell types due to being masked by the dominant types encountered in the analysis[35]. Consequently, bulk sequencing performs well in identifying cis-regulatory elements and predict their functions, but fails to capture cell-type specific signatures in heterogeneous tissues. Single-cell resolution partially solves the previous problems, but raises a series of issues regarding low throughput and, in the case of epigenomic studies, that there are only two copies of genomic DNA within diploid cells, which is a strong challenge for the detection efficiency of the epigenome. A notable pitfall of the single-cell profiling assays consists in the low coverage of genomic DNA, which confronts researchers with making a compromise between data sparsity and high cell throughput[36]. Such questions are continuously addressed by developing new strategies, cell sorting methods and protocols that aim to reduce the number of errors and increase the assay's efficiency. These spots are still resolved by the higher genomic coverage of bulk sequencing, thanks to its greater sequencing depth that captures subtle epigenetic modifications within regulatory regions. Certain features prove to be especially useful in the context of homogeneous cell populations, where averaging signals provide reliable data regarding DNA methylation status and chromatin accessibility. Nonetheless, bulk epigenomic assays come with the advantages of being cost effective while being a more standardized option that has consistent reproducible results across laboratories. Thus, bulk sequencing offers a more affordable alternative for performing large-scale procedures, with less technical noise and without requiring living cells[3,35,37]. The full landscape of regulatory genomics can be described only through the complementarity between bulk and single-cell sequencing methods, bulk analysis bringing a broad perspective, whereas single-cell studies increase the resolution to the point of interpretation of individual epigenetic signal's relevance (see **Table 1** for a brief comparison between bulk and single-cell analyses).

Further challenges in epigenomics come from the area of computational resources. Deep learning models, as a subset of AI, are promising tools for omics research thanks to their architectures that resemble the human cortex. These intricate artificial

Table 1. Comparison between bulk and single-cell sequencing methods used for epigenomics[35,36,37]

Bulk sequencing	Single-cell sequencing
• Faster, less time consuming • Less expensive • Established pipelines • Lower technical noise • Renders an average signal of the population, revealing the dominant regulatory trend • Fails to reveal heterogeneity of the cells within a sample • Cannot tell if multiple epigenetic states originate from different cell types or coexist in a sample • Performs well in identifying cis-regulatory elements	• More expensive in terms of resources and time • Data sparsity • Higher technical noise • Lower per-cell and genomic coverage • Captures tissue heterogeneity • Identifies rare cell populations within a sample • Can infer cell trajectories and epigenetic dynamics • Can reveal cell-specific epigenetic profiles

neural networks present processes similar to cognition that enable inferences regarding complex, non-linear relationships that establish within biological systems. Suitable tasks for DL include dealing with high-dimensional, sparse and noisy data encountered in omics. While these advantages encourage the integration in omics-related applications, the gray areas in AI research highlight the importance of conflicting findings related to DL platforms. Furthermore, these frameworks have been often called 'black boxes' due to the lack of interpretability- the complex multi-layered connections, together with the large number of parameters and non-linear architectures render these systems as incomprehensible to most human operators. The central issue is defined as the impossibility to trust the model; the predictions cannot be validated due to not tracking the reasoning behind the DL models' output[38].

The high computational demands in epigenomics catalyze a quest for advanced resources to deal with the intricate regulatory networks. Beyond AI platforms, quantum computing aims to address the remaining challenges with its ability to model complex interactions and efficiently extract patterns from high-dimensional datasets. This promising technology might be of invaluable help in transforming single-cell multi-omics in successful large-scale studies. A combined approach in which quantum kernels perform combinatorial optimization, relevant feature selection, dimensionality reduction and cell clustering, pattern recognition, whereas DL models focus on downstream prediction tasks. Such hybrid frameworks may significantly contribute to refined epigenomics patterns identification, including epigenetic states, enhancer-promoter interactions, disease-associated regulatory signatures. Although some applications sound as mere speculations at the moment, being limited by technical noise and hardware constraints, the future suggests huge improvement in algorithms' performance for gene expression predictions and chromatin organization studies by designing quantum-enhanced DL models[39,40,41]. Researchers push evolution forward at a very alert pace to get rid of current shortcomings that still hide essential aspects from the epigenomic landscape and from other omics branches. Future exploration will certainly delve deeper into the 3D genome organization, dynamic epigenetic traits and cell lineage tracing, while emphasizing the single-cell technologies' essential role in uncovering heterogeneity. Research may also consolidate the position of quantum-enhanced DL platforms performing quality control, reducing batch, dropout effects and dimensionality, overall resulting in highly accurate predictions.

4. Conclusion

Personalized medicine approaches benefit significantly from the conjoined efforts of bioinformatics and genetics to offer groundbreaking results that will contribute to new diagnostic and therapeutic tools. The multimodal analysis performed by various DL architectures enable simultaneously accounting for many parameters that guide towards the creation of individualized panels of biomarkers. Enhanced diagnostic and prognostic accuracy may furnish a better outcome for more patients and shorten the time spent for identifying the disease and the correct treatment plan[42]. Epigenomics, in conjunction with revolutionary computational tools, outlines biomarkers that might serve as cutting-edge diagnostic tools or as therapy targets in the near future. With these coordinates in mind, the synchronous development of both advanced omics and AI-based frameworks or other analytical resources uncover a new path towards precision medicine. On this premise, continuous research aims to build patient-tailored healthcare models that will suit the particular needs of each person.

Conflict of Interest

The authors declare no conflict of interest.

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