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Computational-Based Approaches in Epigenetic Research: Insights from Computational Tools, Mathematical Models, and Machine Learning Methods

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Abstract

Understudying epigenetics underlying mechanisms is essential. Studies have indicated functional roles of epigenetic events, including DNA methylation and histone modifications, in human disease, stem cell growth and development, aging, response to environmental stresses, and species evolution. High-throughput sequencing techniques alongside routine experimental approaches have rapidly produced a bulk of data that the major part of them remained unprocessed. To analyze, interpret, and process of these data, availability of efficient computational methods is critical. Epigenetic data analysis is complex and difficult because these data contain multi-layer set of information. The methods implemented to this purpose must be able to handle massive data of experimental works and process the epigenetic layers. Furthermore, the methods must be capable of integrating multiple modifications and their combination effects on chromatin conformational structure and consequently the expression network of genes. In this study, we briefly reviewed challenges in the way of the computational epigenetics, the latest reported methods, and significant biological results derived from Appling computational-based methods on epigenetic data.

Keywords: Bioinformatics; Computational epigenetics; Data analysis; DNA methylation; Epigenomics

Introduction

The importance of epigenetics in biology and medicine is clear to every scientist who works on pertinent fields. Epigenetics refers to any mechanisms by which gene expression is altered without any changes in DNA sequence. Many studies have found association of epigenetics with many diseases, stem cell functions, immunology, growth and development, responding to stress, species conservation, evolution, aging etc. [1-3]. These implications of epigenetics events have revealed an essentiality of understanding epigenetics and epigenomics-epigenetic changes across the genome- especially its underlying molecular mechanisms.

DNA methylation is a well-known epigenetic process in which a methyl group (CH_3) is added on cytosine bases. The process particularly occurs at CpG islands where cytosine bases are highly concentrated. The multiple DNMT proteins mediate adding the methyl group at cytosine bases. Histone modification is another epigenetic process. The modifications of histones such as methylation, acetylation, phosphorylation, sumoylation and ubiquitination, alter the genome structural configuration, leading to gene expression changes at affected regions. Actually, the configurational changes provide/limit transcription factor accesses. Electrostatic interactions between histones and DNA are underlying powers to create structural changes [3-5]. The studies conducted during the past 20 years have indicated that the molecular mechanisms of causes and consequences of epigenetics are more complex and there is need to investigate on many unknown prospects.

Some of the common experimental methods include ChIP (ChIP-on-chip combine chromatin immunoprecipitation) that is a method to detect differences between sample and control DNA. In this method, formaldehyde is first used to cross-linking DNA-bound proteins to the DNA. Then, histones are fragmented into about 500 base pairs, that each of these fragments with epigenetic modifications separated by antibodies. Finally, the nucleotides are released from the separated fragments and used to be hybridized with microarray data to find epigenetic modifications [6]. MeDIP (ChIP-on-chip that is called methyl-DNA immunoprecipitation) is a varied method of ChIP in which antibodies are used against methylated cytosines. This method is widely used to find DNA methylation [7]. ChIP-seq uses high-throughput DNA sequencing instead of hybridization process and is more accurate and cheaper than its primary forms, described earlier [8]. For more methods and detailed information refer to review by [9]. Bisulfite sequencing is a high-resolution method that is able to detect DNA methylation patterns. In spite of high resolution and efficiency, this method is expensive [10]. These methods integrated with several protocols have widely been used. The majority of protocols to assess epigenetic events are based on some of the following basics: (i) techniques to inhibit DNA methylation and assess DNA methylation activity, (ii) chromatin immunoprecipitation based protocols, (iii) *in vivo* RNA-Protein interaction assessment, and (iv) knockdown of histone deacetylases [11]. Besides experimental works, bioinformatics tools and computational biology have made remarkable advances in elucidating epigenetic events. Various bioinformatic tools and computational methods have been developed for managing, handling, and analyzing different epigenetic data and many researches have been conducted in this context (Figure 1).

The importance of computational-based methods in the epigenetic fields has essentially been revealed after emerging high-throughput sequencing techniques that have accumulate the bulk of unannotated

data. Indeed, computational methods are need not also for interpreting data resulted from experimental works but for genome-wide analysis of the genome for specific sequences responsible for epigenetic modifications. Increasing large-scale dataset has enriched analysis related to epigenetics, but also it has made it more complex and further outline crucial roles of computational tools in this regard. Here, we briefly reviewed the computational epigenetics and the latest bioinformatic methods developed to study epigenetic causes and consequences.

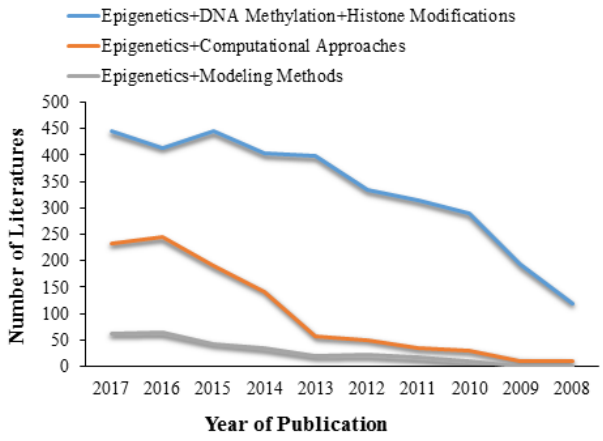

Figure 1: Number of literatures related to epigenetics and computational approaches published between the years 2008 to 2017. The keywords used for search were epigenetics, DNA methylation, histone modifications, computational approaches, and modeling methods. A number of hits for epigenetics + machian learning search were 65 literatures. The search was performed at PubMed.

The Challenges and Opportunities of Computational Epigenetics

The combination of computer science, statisticians, physicists, and computational biology constitute computational epigenetics. The aim of computational epigenetics is to design and develop computational-based methods and programs to analyze data resulted from experimental works on epigenetics [12]. Data of epigenetic researches encompass multiple layer of regulatory mechanisms and clues that must mainly be extracted from high-throughput sequencing techniques [13]. This makes complexes and difficulties to establish computational-methods. However, the methods must address available issues related to (1) the experimental methods such as background read problem in ChIP-seq [14], (2) analytic approaches [15], (3) methods to integrate interplay of other compounds, such as microRNAs, with epigenetic regulation [16], and (4) the biased data resulted from the experimental mythologies such as profiling DNA methylation by MBD-seq [17]. In addition, there is more space for computational methodologies to open insight on protein-protein interactions, to decrease cost of epigenome mapping, to theoretically modeling of epigenetic mechanisms, and to improve statistical genome browsers [18].

Data Sources

Databases are one of the main places that information related to epigenetics could be accessed. MethDB contains information about DNA methylation and methylation patterns in many species. PubMed contains text-type file of more than thousands scientific articles related to methylated and other types of epigenetic modifications. REBASE is a database that connected to GenBank database. Genes responsible to encode DNA methyltransferases have deposited in this database. Epigenetic data related to human chromatin and disease could reach in MeInfoText, MethPrimerDB, The Krembil Family Epigenetics Laboratory and MethyLogiX DNA methylation database. Of other useful databases, we could mention to The Histone Database, ChromDB, CREMOFAC, The National Human Genome Research Institute (NHGRI)'s Histone Database, The National Center for Biotechnology Information (NCBI)'s Gene Expression Omnibus (GEO), The Gene Normal Tissue Expression (GeneNote) database, DNA Data Bank of Japan (DDBJ), and The BloodExpress database [12].

Computational Analysis of Epigenetic Data

There is a variety of computational-based approaches to analyze, modulate, and predict epigenetic modifications in given sequences. In the case of detecting DNA methylation, efforts have mainly devoted to discover of methylated CpG islands and allele specific cytosine methylation. The CG dinucleotides are mostly scarce throughout genome, especially in vertebrates [19] and mainly clustered in the regions called CpG islands (CGIs). These rich regions with CG dinucleotides, CGIs, are interestingly located at the promoter of coding and non-coding genes, making them very attractive for researchers [19,20]. Because altering DNA methylation patterns of CGIs play essential roles in controlling the gene expression and silencing in various biological processes, such as X-chromosome inactivation, imprinting, silencing of intragenomic parasites [21,22] and especially in the epigenetic causes of cancer [21]. Due to CGIs essential implications in mentioned processes, multiple algorithms (either specific species or general purpose) have been developed to identify CGIs in the genomes. In this context, Gardiner-Garden and Frommer were the first who used an algorithm to study CGIs and G+C content in the genome of vertebrates. Subsequently, many other methods based on different algorithms had been developed [23-25]. Of these methods, artificial neural networks (ANN) and support vector machines (SVM) have broadly been used to analyze DNA methylation. Marchevsky et al. trained ANN with molecular data in order to classify lung cancer cells based on DNA methylation marker. They provided evidence that ANN could be used as a powerful approach for detecting DNA methylation. Das et al. indicated that SVM could predict methylation status of CpG regions with accuracy of 86%. They used this method to depict methylation patterns of all 22 human autosome chromosomes. The methods such as hidden Markov models (HMM), logistic regression, K-nearest neighbors and decision trees have also been used for this purpose [26,27], for example Barazandeh et al. disclosed significant correlations between CGI density and genomic features such as chromosome size, GC content, ObsCpG/ExpCpG, gene density and recombination rate in cattle. However, these methods were suffering from several disadvantages. First, these methods lacked systematic selection methods for a length threshold [28]. Second, they were unable to detect weak CpG islands [29]. Third, they were sequence-based to identify CpG islands and failed to distinguish between genuine CpG islands and CpG-rich regions [30]. To overcome these

drawbacks, Bock et al. suggested epigenome prediction method and used integrates DNA methylation, polymerase II preinitiation complex binding, histone H3K4 di- and trimethylation, histone H3K9/14 acetylation, DNase I hypersensitivity and SP1 binding as criteria to map CpG islands. Their method could distinguish between weak and stronger CpG islands and use feathers of genomic DNA sequences and epigenome [31].

In respect to modifications of CGIs, the methylation is not only modification. Studies on the mammalian genome have demonstrated that in addition to methylation, there are other forms of modification including hydroxymethylation, formylation, and carboxylation [32,33]. The specific roles of these type modifications are still little known, but it has been hypothesized that these types might be intermediate steps during methylation and demethylation processes or even they may have own implication in diseases [34,35]. Furthermore, the three high-resolution structure of chromatin revealed two methylations, two hydroxymethylations, and five formylations have effects on DNA dodecamers, while methylation and hydroxymethylation alone have not any effects on the geometry of DNA [36,37]. These imply this fact that for fully understanding of CGI modification effects on chromatins structure; consequently, altering expression of genes it is critical that analyzing methods must include all of the modification possibilities. One of the computational methods that meet these criteria is reported by Krawczyk et al. in which they extended Natural Move Monte Carlo to simulate the conformation changes of chromatin as consequence of epigenetic modifications [38].

In the case of prediction, modeling and analysis of histone modifications, some methods have reported, such as simplified stochastic model [39], genome-wide chromatin analysis [40], and genome-wide mapping [41]. From the machine-learning methods have been used to detect histone modifications (acetylation, methylation, phosphorylation) we can mention to HMM approach [42], using chromatin signatures [43], model based on the prediction of pH-dependent aqueous solubility [44], and HMM based on the domain-level behavior [45]. Benveniste et al. recently showed that histone modification prediction could achieved from knowledge of transcription factor binding at both promoter and distal regulatory elements. Furthermore, the methods such as QSAR analysis, homology modeling, and molecular docking methods have used for detecting histone modifications [46-48]. These tools have well been used for deciphering epigenetic effects on various biological processes. Furthermore, using interaction between epigenetic, genetics and environment can improve estimation of breeding values and reduce their biases [49].

The histone code hypothesis [50] articulates that the roles of histone post-translational modifications (PTM) are well descripted when the combinations and sequences of histone PTMs are accounted. Based on this hypothesis, several computational methods were developed for identification of histone modifications. ChromaSig and ChromHMM are two computational methods have been developed for this purpose [51,52]. These methods are based on multivariate Hidden Markov Models and are able to show histone modifications and chromatin statues. Given that only subsets of the histone PTM combinations take place in nature, the later approaches were developed based on partial correlations and maximum entropy modeling. These methods have been used for identification of pairwise and high-order interactions between chromatin factors [53].

Computational Epigenetic Research

Computational methods have remarkably helped to explore molecular mechanisms of epigenetics and its association with biological processes. Cancer is one of the field that computational epigenetics has widely been used. It has been indicated that DNA methylation patterns in cancer are variable and tumor type specific. To elucidate DNA methylation pattern in cancer, several computational approaches have been used, such as using regression models to analyze DNA methylation profile [54], using SVM to analyzed DNA methylation in tumor class [55], and using Manhattan distance and average linkage algorithms for CpG island pattern analysis of human colorectal tumors [56].

Stem cell is another field that computational epigenetics have widely used. Recent studies have revealed unique epigenetic profiles of embryonic stem cells, as reviewed by Spivakov and Fisher. Walker et al. formulated novel networks that indicate gene response of key developmental regulators in embryonic stem cell and could predict the outcomes of genetic manipulation in this network. They used temporal expression microarray analyses and known genome-wide transcription factor to construct the networks. In another study, Ringrose et al. used computational-based method to successfully identify 167 candidate Polycomb/Trithorax response elements (PRE/TREs). These elements are involved in development and cell proliferation [57-59].

Neurodegenerative and autoimmune diseases are two another important diseases that have been studied using a computational based method to find epigenetic factors responsible for the diseases [60]. Irin et al. in this study proposed a computational method able to explain the functional consequences of epigenetic modification. The method, called BEL (Biological Expression Language), is capable of integrating literature-derived information into network model. Moreover, it is possible to apply Reverse Causal Reasoning (RCR) algorithms, which support identification of mechanistic hypothesis from related network model.

Concluding Remarks and Outlook

Many high-throughput sequencing technologies open new era for epigenetic research. To handle millions of these data, many computational tools have been developed. There are, however, issues that the computational tools have to address. Computational methods must be especially able to integrative analysis of epigenetic layers. These methods could remarkably improve our knowledge of complex regulatory processes and interconnections by which epigenetics works. It has been observed that even small networks with few components in epigenetic events tend to behave in complex and unexpected manners. Therefore, there is need to build up systematic and focused modular approaches to elucidate fundamental understanding of epigenetics. Some methods developed for analyzing literature-derived data are not efficient in showing epigenetic modifications at gene level so extending these methods should be considered.

It is expected that in the future the computational methodologies shift for being able to (i) interpret data so that can be used in quantifying the disease risks and driving therapeutics, (ii) draw meaningful inferences of epigenetic modifications in diseases, (iii) develop novel approaches for new powerful epigenome-editing and high-throughput experimental methodologies, and (iv) integrate the combination of the computational methods, especially machine learning approaches. It could likely be result to deepen our understanding of epigenetic mechanisms.

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