Deep Neural Network for Analysis of DNA Methylation Data

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Abstract

Many researches demonstrated that the DNA methylation, which occurs in the context of a CpG, has strong correlation with diseases, including cancer. There is a strong interest in analyzing the DNA methylation data to find how to distinguish different subtypes of the tumor. However, the conventional statistical methods are not suitable for analyzing the highly dimensional DNA methylation data with bounded support. In order to explicitly capture the properties of the data, we design a deep neural network, which composes of several stacked binary restricted Boltzmann machines, to learn the low dimensional deep features of the DNA methylation data. Experiments show these features perform best in breast cancer DNA methylation data cluster analysis, comparing with some state-of-the-art methods.

Keywords: DNA Methylation, beat-value, deep neural network, restricted Boltzmann machine

1. Introduction

DNA methylation, occurring in the context of a CpG dinucleotide, is a kind of epigenetic modification in human genome, which can be inherited through cell division \(^1\). Some special methylation patterns are found in many genetic diseases including various types of cancer \(^48\). Due to the role of methylation patterns in the etiology of complex diseases, DNA methylation analysis becomes a powerful tool in cancer diagnosis, treatment, and prognostication.

The high throughput methylation profiling technology, \(e.g.,\) the Illumina methylation platform, has been developed to survey methylation status of more than 1500 CpG sites associated with over 800 cancer-related genes \(^49\), which makes it is easily to measure genome-wide from limited amounts of
DNA and allows measurements in clinical specimens [50]. Currently, there is a strong interest in studying how the methylation profiles can be used to distinguish different subtypes of the tumor. These researches perform unsupervised clustering of large-scale DNA methylation data sets [51].

Formerly, the clustering work focused on the sequence level. Recently, the exact value levels of methylation expression has been fully considered and attracts more and more attentions. The beta-value, which means the ratio of the methylated probe intensity and the overall intensity (sum of methylated and unmethylated probe intensities), is usually used to express the methylation level [52]. Beta-value is quantified naturally bounded between 0 and 1. Under ideal conditions, a value of 0 means the CpG site is completely unmethylated and the value of 1 indicates the site is fully methylated [52].

Due to the unique non-Gaussian characteristics, traditional Gaussian distribution-based clustering methods are not be appropriate for DNA methylation data analysis [53]. In order to make the methylation data range satisfy the definition of Gaussian distribution, some transformation methods were proposed, such as the M-value method which uses the logit-transform to change the feature range to \((0, \infty)\) [52]. However, these transformations may cause worse inference and the mathematical transformation on methylation data is lack of the support of the biological significance [53]. Hence, more researchers tend to deal with the beta-value directly by using beta mixture model [52, 54, 55, 56]. The DNA methylation expressions can be modeled by a mixture of beta distributions. Unfortunately, estimation of the beta mixture model does not have an analytically tractable solution and the analysis based on it cannot be derived in an explicit form. Thus, many approximate solution methods, such as variational Bayes inference [57] and Gibbs sampling [58], have been adopted to solve this problem.

Moreover, the extremely high dimensions of the methylation data also yield many practical problems in pattern analysis. Generally speaking, we conduct dimensionality reduction work before cluster analysis. However, the traditional method, e.g., principal component analysis (PCA) [59] and nonnegative matrix factorization (NMF) [60], are all based on the Gaussian distribution assumption. The bounded support property cannot be preserved during the transformation. Hence, the statistical properties of the non-Gaussian DNA methylation data sets cannot be efficiently described by these existing dimension reduction methods.

Recently, deep learning algorithms, which are making artificial intelligence smarter for vision and speech, have been used to solve the bioinformatic problems. It provides an efficient tool for analyzing considerable high
dimensional biomedical data. By unsupervised or semi-supervised training, an interactional multilayer complex neural networks can be build to automatically extract the unobserved deep information hidden in the unisy biomedical data. The deep neural network has been applied to predict how genes were spliced together in mice [61], assess the state of Parkinson’s Disease [62], denoise the ECG signals, and many other biomedical researches [63].

Inspired by these work, we use an auto-encode deep neural network model to carry out the dimensionality reduction task in this paper [64]. The network is composed by several stacked binary restricted Boltzmann machines (RBM). The RBM is a probabilistic graphical model that can be interpreted as stochastic neural network [65], the input and output of binary RBM are regarded as probabilistic values and naturally bounded in [0, 1]. Such properties have similar manner with the DNA methylation data. Thus, this model is suitable to analyze the methylation data.

In the experimental part, we examine the effect of DNA methylation data analysis based on deep neural network (DNN). Firstly, we check the dimension reduction effect. By high-dimensional data visualization technology, we can observe that the features with low dimension can distinguish cancer from normal samples efficiently. Secondly, we conduct some unsupervised clustering analysis using the features extracted from the DNN model. The results demonstrate that cancer and healthy samples can be efficiently clustered into different groups based on the DNN-based features.

The rest of the paper is organized as follow: we introduce the adopted DNN structure in Section 2. The experimental results are presented in section 3, in which we describe the DNA methylation data sets and illustrate the DNA data analysis results. Finally, we draw some conclusions in section 4.

2. Deep Neural Networks Structure for DNA Methylation Data Analysis

Since 2006, deep learning method has been widely used in many fields of science researches [66–68]. Many different deep learning models are applied for different applications, e.g., deep neural networks (DNN) and convolutional neural network (CNN) [69]. DNN has a classical auto encode (AE) structure [67] which can be used to extract deep feature automatically. An AE is composed with several stacked RBM, as shown in Fig.1. (a). The RBM is an undirected graphical model that defines the distribution of visible units using binary hidden units. The inner structure of RBM is shown in
(a) Deep neural networks structure.  
(b) Inner structure of RBM.  

Figure 1: Illustration of a stacked RBM.  

**Fig.1.** (b). The joint distribution of binary visible units and binary hidden units is written as follows:  

\[ P(v, h) = \frac{1}{Z} \exp(-E(v, h)), \]  

(1)  

\[ E(v, h) = -\sum_{i=1}^{D} \sum_{k=1}^{K} v_i W_{ik} h_k - \sum_{k=1}^{K} b_k h_k - \sum_{i=1}^{D} c_i v_i, \]  

(2)  

where \( v \in \{0,1\}^D \) are the visible (input) units, and \( h \in \{0,1\}^K \) are the hidden (output) units.  \( Z \) is the normalizing constant, and \( W \in \mathbb{R}^{D \times K} \), \( b \in \mathbb{R}^K \), \( c \in \mathbb{R}^D \) are the weight matrix, hidden, and visible bias vectors, respectively.

Since there are no connections between the units in the same layer, visible units are mutually conditionally independent given the hidden units, and
Table 1: Comparisons the clustering effect based on different feature extraction and unsupervised clustering methods.

| Method     | Error rate(%) | Cancer→Healthy | Healthy→Cancer |
|------------|---------------|----------------|----------------|
| PCA+ k-means | 5.15          | 7              | 0              |
| PCA+ GMM   | 5.88          | 8              | 0              |
| PCA+ SOM   | 4.41          | 0              | 6              |
| NMF + k-means | 8.82        | 12             | 0              |
| NMF + GMM  | 12.5          | 17             | 0              |
| NMF + SOM  | 3.68          | 1              | 4              |
| DNN + k-means | 5.15         | 7              | 0              |
| DNN + GMM  | 5.15          | 7              | 0              |
| DNN+SOM    | **2.94**      | **4**          | **0**          |

vice versa [70]. The conditional probabilities of the RBM can be written as follows:

\[ P(v_i = 1|h) = \sigma(\sum_k W_{ik} h_k + c_i), \]  

\[ P(h_k = 1|v) = \sigma(\sum_k W_{ik} v_i + b_k), \]  

where \( \sigma(x) = \frac{1}{1+e^{-x}}. \)  

Training the RBM corresponds to maximizing the log-likelihood of the data with respect to parameters \( \{W, b, c\} \). Although the gradient is intractable to compute, contrastive divergence [65] can be used to approximate it.

In training process, each RBM can be trained independently and the output of the bottom RBM can be used as the input data of the upper RBM. After getting all the parameters for each layer, we can get a DNN as shown in Fig. 1. (a) to carry out feature extraction and dimension reduction.

Because the input unit is binary, the input data sent to the input unit should be bounded from 0 to 1. This peculiarity just adapts the characteristic of DNA methylation data. The output getting from equation 4 are also bounded, which makes the features finally extracted from the top layer are still in accordance with the characteristics of methylation data (in \([0, 1]\)).

In this paper we built a DNN with 4 layers. The (input, output) unit numbers of the bottom 3 layers were set as \{(5000, 1000), (1000, 500), (500, 250)\}, respectively. The top layer’s output units number was set as \{10, 20, 30, 40, 50, \}
60, 70} to extract the best feature of the input data. The analysis of results are shown in Section 3.

3. Experimental Results and Discussions

The DNA methylation data were obtained from the Gene Expression Omnibus (GEO) website \[71\]. GEO is a public functional genomics data repository supporting MIAME-compliant data submissions. In this section, we used the dataset GSE32393 to evaluate the dimension reduction and unsupervised clustering effect \[72\]. This dataset include 136 women breast tissues samples with 113 breast cancers samples and 23 non-neoplastic samples. From each sample, we obtained approximately 27,578 DNA methylation features. In order to reduce the interference of the noise data we selected 5,000 features with the highest variance across the 136 samples as the experimental data.

The selected 5,000 dimensional features were sent to the DNN described in Section 2 to realize further dimension reduction. In order to find the best feature dimension, we set the output units number as \{10, 20, 30, 40, 50, 60, 70\}. Then these dimension reduced features were clustered by the self-organizing feature maps (SOM) methods \[78\]. After intensive experiments, we found out when setting the cluster number \(k = 5\) and the feature dimension reduced to 30, the best results can be achieved.

Comparing the dimension reduced effect between DNN and some other traditional methods, we also reduce the 5,000 features into 30 dimension using traditional PCA and NMF method \[79\], respectively.

In order to visually assess the effect of feature selection, we adopted the t-distributed stochastic neighbor embedding (t-SNE) method to visualize the high-dimensional data in two-dimensional space \[73\]. t-SNE is a nonlinear dimensionality reduction technique which has been used in a wide range of applications, including computer security research, \[74\] music analysis \[75\], cancer research \[76\], and bioinformatics \[77\]. It is particularly well suited for embedding high-dimensional data into a space of two or three dimensions, which can then be visualized by a scatter plot. Especially, it models each high-dimensional object by a two- or three-dimensional point in such a way that similar objects are modeled by nearby points and dissimilar objects are modeled by distant points.

The visualization results are shown in Fig.2 and it is clearly illustrated that the cancer (red circle) and healthy (black star) points in Fig.2. (b) are better separated than those in Fig.2. (a). This indicates that feature selection can potentially improve the clustering performance. Fig.2. (c),
Table 2: Comparisons the clustering results between DNN+SOM method and some other mixture model-based methods.

| Method                  | Error Rate(%) | Cancer→Healthy | Healthy→Cancer |
|-------------------------|---------------|----------------|---------------|
| PCA + VBGMM             | 6.62          | 9              | 0             |
| BGNMF + RPBMM          | 3.68          | 4              | 1             |
| BGNMF + VBBMM          | 3.68          | 4              | 1             |
| SC + VBWMM             | 5.15          | 7              | 0             |
| DNN+SOM                | **2.94**      | **4**          | **0**         |

(d) and (e) showed the dimensional reduced effect of PCA, NMF, and DNN, respectively. It was shown clear that the DNN method can capture the features of DNA methylation data better than the PCA and NMF method, which means that the DNN features are more effective for the clustering analysis.

In order to make fair comparisons, we also applied the k-means, the Gaussian mixture model (GMM), and the SOM method to cluster the features extracted by PCA, NMF, and DNN methods, respectively. The results were shown in Table 1. It could be observed that the DNN features performs the best among all the clustering methods, and the SOM clustering method performed better than the others.

Figure 2. (f) shows the visualization clustering result of the 30 dimensional DNN features based on the SOM method. All the samples were clustered into 5 groups and all the 23 healthy samples (red star) were grouped in group 1 (the healthy group, denoted in red), only 4 cancer samples (red triangle) were allocated in this group by mistake. The group 2, 3, 4 and 5 were cancer group and none of the healthy samples was clustered in them.

We also compared the DNN+SOM method with some other mixture model-based methods including PCA+VBGMM (variational Bayesian Gaussian mixture model) [57], BG-NMF (Beta-Gamma Nonnegative matrix factorization) + RPBMM (recursive partitioning Beta mixture model) [79], BG-NMF + VBBMM (variational Bayesian estimation framework for Beta mixture model) [55] and SC (spectral clustering) + VBWMM (variational Bayesian estimation of Watson mixture model) [53]. The result was shown in Table 2 (some result were from paper [53]). We can see that, compared with the complex probabilistic mixture models, the DNN is a simple yet effective model which can get the best result among all the compared methods.
4. Conclusions

The DNA methylation level can be used to distinguish cancer gene from normal gene. However, the high dimensionality makes it hard to be analyzed directly and analyzed. Meanwhile, the non-Gaussian properties of the data make many conventional dimension reduction methods do not work well. In this paper, we adopted a dimension reduction method based on deep neural networks (DNN). The DNN is built by 4 stacked binary restricted Boltzmann machines (RBM). The binary input and output units of the RBM fits the DNA methylation data’s bounded support property well and the self-learning ability can extract the low dimensional features automatically. The experiment results demonstrate the low dimensional features getting from DNN can separate the normal samples from the cancer samples effectively. Compared with some recently proposed probabilistic mixture model-based methods, the DNN-based method shows significant advantages.

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Figure 2: (a) Visualization of the original 27,578 dimensional data; (b) Visualization of the selected 5,000 dimensional data; (c) The visualization of 30 dimensional features extracted by PCA method; (d) The visualization of 30 dimensional features extracted by NMF method [79]; (e) The visualization of 30 dimensional features extracted by DNN; (f) Clustering result of the 30 dimensional DNN features based on SOM method.