02-510/710: Computational Genomics, Spring 2025

HW4: Dimension reduction and motif-finding

Version: 1
Due: 23:59 EST, Apr 7, 2025 on Gradescope

Topics in this assignment:

1. Dimension reduction
2. Motif-Finding

What to hand in.

- One write-up (in pdf format) addressing each of following questions.
- All source code. If the skeleton is provided, you just need to complete the script and send it back. Your code is tested by autograder, please be careful with your main script name and output format.

Submit the following file which contain the completed code and the pdf file to gradescope separately.

./S2025HW4.pdf

Please note that all the solutions must be your own. We will check for plagiarism after the final submission.

1. [**40 pts**] **dimensionality reduction**

   In this problem, we will explore linear and nonlinear dimension reduction methods. Assume you have a high-dimensional dataset from gene expression, with each sample containing the expression levels of 1000 genes. The dataset is known to be divided into two main classes (e.g., tumor and normal cells), but their specific characteristics are not yet clear. Data can be find from provided_data/gene_expression.csv. Please answer the following questions.

   (a) Data Preparation and PCA. Standardize the gene expression data for each sample. After applying PCA, calculate the explained variance ratio of the first two principal components.

   Solution

   (b) There are 2 key hyperparameters for t-SNE: perplexity and learning rate. Please briefly describe their potential impact on the dimensionality reduction results.

   Solution

   (c) t-SNE Implementation. Implement t-SNE on the standardized gene expression data. Experiment with 3 different perplexity values (e.g., 5, 10, 50) and a fixed learning rate (200). Please visualize the results using scatter plots. Additionally, use a quantitative metric such as the silhouette score to evaluate which perplexity setting provides the best separation between "normal" and "tumor" samples.

   Solution

2. **[60 points] Motif Finding**

In lecture we were introduced to an algorithm used for finding motifs in DNA sequences based on Expectation Maximization (EM). This algorithm forms the basis of the MEME Suite (**M**ultiple **E**M for **M**otif **E**lucidation), one of the most widely used softwares in genomics. Several good papers are available for understanding the algorithm, including the ones here and here.

Consider a biological motif of length W, $M = (M_1, \ldots, M_W)$, where $M_i \in \{A, C, G, T\}$. Our model for biological motifs is that each M_i is a Multinoulli-distributed random with its own probability distribution over the nucleotides A, C, G, and T. We can equivalently represent this motif as a position weight matrix $(M)_{ij}$, for which

$$M_{ij} = \mathbb{P}(M_j = i),$$

where $j = 1, \ldots, W$ and $i \in \{A, C, G, T\}$. Consider the PWM below for a motif of length $W = 6$:

$$M = \begin{array}{c} \\ A \\ C \\ G \\ T \end{array} \begin{array}{c} \begin{array}{cccccc} M_1 & M_2 & M_3 & M_4 & M_5 & M_6 \end{array} \\ \begin{bmatrix} 0.8 & 0.1 & 0 & 0.9 & 0 & 0.3 \\ 0 & 0.4 & 0.05 & 0.03 & 0.1 & 0.2 \\ 0.2 & 0 & 0.95 & 0.02 & 0.1 & 0.1 \\ 0 & 0.5 & 0 & 0.05 & 0.8 & 0.4 \end{bmatrix} \end{array} \tag{1}$$

One of the key assumptions we make when modeling motifs is that $M_i \perp M_j$ for $i \neq j$; that is, the distributions of the nucleotides in each position of the motif are independent of one another.

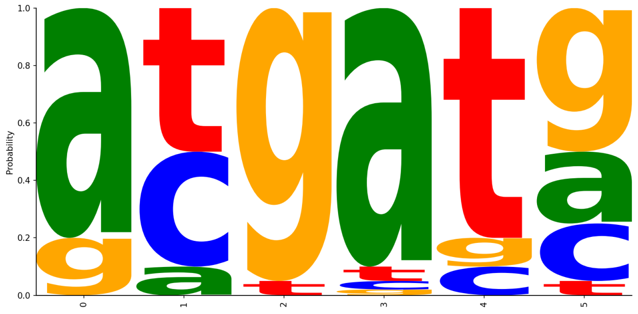
(a) Find the probability $\mathbb{P}(M = ACCTTA)$.

Solution

(b) Provide the Consensus Sequence corresponding to the PWM above; i.e., the sequence $m = (m_1, \ldots, m_5)$ such that $\mathbb{P}(M = m)$ is maximized.

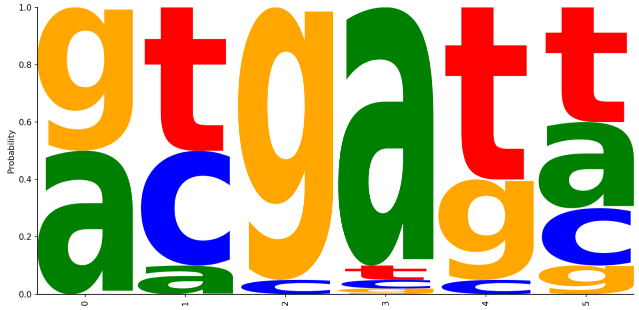
Solution

(c) Which of the following sequence logos accurately represents the PWM? Briefly describe why the other logos are incorrect.

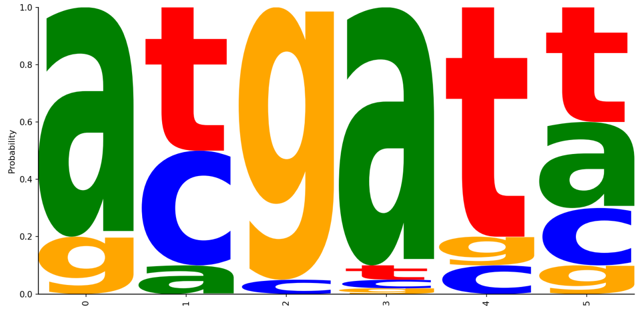


1)

2)



3)



Solution

(d) The height of the sequence logo is often scaled by the information content at a given position i. The information content is given by $R_i = log_2(4) - (H_i + e_n)$, where H_i is the entropy of the position, and $H_i = -\Sigma_j[M_{i,j} * log_2 M_{i,j}]$.
Which position in the PWM has the greatest entropy? How is entropy related to conservation?

Solution

(e) One of the advantages of the MEME suite is that, for a given DNA sequence, it can detect the most likely positions to find the motif learned in the PWM. To do so, it converts the PWM into a matrix of log likehood ratios using the formula $LLR(s) = log_2[\frac{Pr(s|M)}{Pr(s|M_{bg})}]$. The log likehood score that a given position i is a start position of the motif is equivalent to $S(X) = \sum_{i=x_i}^{i=x_i+w} log_2[\frac{M_{ij}}{M_{ij}^{bg}}]$.

One method of determining if a position is included in the motif is to use a decision rule. For example, we could use : 'X is a true instance of M if $LLR(X) > 0$, or equivalently, if $\mathcal{S}(X) > 0$'. Is this a statistically sound approach? Why or why not?

Solution

(f) An alternative approach to determine where or not a position i contains the motif is to use hypothesis testing to calculate the p-value for S(p). We can define the hypotheses as:

- H_0: X is drawn from the background distribution M^{bg}
- H_1: X is drawn from the motif distribution M

Briefly describe a method for calculating the test statistic. Hint: one definition of p-value is the probability of receiving a value as or even more extreme than S(X) under the null hypothesis.

Solution