Kullback-Leibler Dissimilarity of Markov Models for Phylogenetic Tree Reconstruction

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ABSTRACT

In this paper, we introduce the Kullback-Leibler dissimilarity measure of Markov-chain models for unaligned DNA sequences with application to the phylogenetic tree reconstruction of complete mammalian mitochondrial genomes. The tree obtained by our approach is generally in agreement with those obtained from other methods. Our proposed method is computationally efficient and very easy for computer implementation.

1. INTRODUCTION

The study of similarity/dissimilarity comparison of DNA genomic sequences is a challenging and important area of computational biology and bioinformatics [8]. Two distinct bioinformatic methodologies for studying the similarity/dissimilarity of sequences are known as alignment-based and alignment-free methods. The search for optimal solutions using multiple sequence alignment methods [15] encounters difficulty in computational aspect when applied to large biological databases. Alignment-free sequence analysis represents a potential means to these critical limitations of sequence analysis by alignment.

One of the most recent reviews [16] on published methods for alignment-free sequence comparison of biological sequences reports several concepts of distance measures such as the Euclidean distance [2], Euclidean and Mahalanobis distances [17], Markov chain models and Kullback-Leibler discrepancy [17], cosine distance [13], Kolmogorov complexity [7], and chaos theory [1]. Our present work bears some strong similarity to that by Wu *et al.* [17] in which statistical measures of DNA sequence dissimilarity as the Mahalanobis distance and standardized Euclidean distance under Markov chain model of base composition, as well as the extended Kullback-Leibler discrepancy (KLD). The KLD extended by Wu *et al.* [17] was computed in terms of two vectors of relative frequencies of n -words over a sliding window from two given DNA sequences. In contrast, we have derived [10] a probabilistic distance between two sequences using

a symmetrized version of the KLD, which directly compares two Markov models built for the two corresponding biological sequences, for database search of sequence relatedness. We now apply this KLD of Markov models for the phylogenetic tree reconstruction of whole mammalian mitochondrial genomes.

2. KLD OF MARKOV MODELS FOR UNALIGNED DNA SEQUENCES

Let $A = [a_{ij}]$ denote the state transition probability matrix of a discrete Markov process. Each state transition probability a_{ij} is defined as

$$a_{ij} = P[q_{t_n} = S_j | q_{t_{n-1}} = S_i], \quad 1 \leq i, j \leq N \quad (1)$$

where q_{t_n} stands for the actual state at time t_n ($n = 1, 2, \dots$), S_j a state j of a set of N distinct states. In the context of DNA sequences, the number of states $N = 4$ which correspond to the four nucleotide symbols $\{a, c, g, t\}$.

The state transition probabilities are subject to

$$a_{ij} \geq 0 \quad \forall i, j \quad (2)$$

$$\sum_{j=1}^N a_{ij} = 1 \quad \forall i \quad (3)$$

Also let $\pi = \{\pi_i\}$ be the initial state transition distribution where

$$\pi_i = P(q_{t_1} = S_i), \quad 1 \leq i \leq N \quad (4)$$

This Markov chain involves two probabilistic measures A and π , that can be denoted in a compact form as

$$\lambda = (A, \pi) \quad (5)$$

What we have presented above is the first-order Markov model. The higher-order Markov models can be determined as follows. Let $\{\pi_j^{(n=1)}\}$ ($j = 1, 2, \dots, N$) be the absolute (initial) probabilities that the system is in state S_j at t_1 .

Figure 1. Phylogenetic tree reconstruction using KLD of MMs

Given the parameters $\{\pi_j^{(1)}\}$ and A of a Markov chain, the absolute probabilities after a specified number of transitions (n -order) are determined as follows.

$$\pi_j^{(n)} = \sum_i \pi_i^{(1)} a_{ij}^{(n)} \quad (6)$$

where $a_{ij}^{(n)}$ is the n -step or n -order transition probability given by the recursive formula

$$a_{ij}^{(n)} = \sum_k a_{ik}^{(n-m)} a_{kj}^{(m)}, \quad 0 < m < n \quad (7)$$

Let $\lambda_1 = (A_1, \pi_1)$, and $\lambda_2 = (A_2, \pi_2)$ be two Markov models of the two bio-sequences, where each model is constructed by the observed symbols of each corresponding DNA sequence. Our interest is to find a similarity or dissimilarity measure between two Markov models λ_1 and λ_2 . A well-known dissimi-

larity measure between two probability distributions is the Kullback-Leibler divergence (KLD) [4].

Let P_1 and P_2 be two probability distributions on a universe X , the Kullback-Leibler divergence or the relative entropy, denoted as $H(P_1, P_2)$, of P_1 with respect to P_2 is defined by the Lebesgue integral

$$H(P_1, P_2) = \int_X \frac{dP_1}{dP_2} \log \frac{dP_1}{dP_2} dP_2 \quad (8)$$

The discrete version of the KLD defined in (8) is

$$H(p_1, p_2) = \sum_{x \in X} p_1(x) \log \frac{p_1(x)}{p_2(x)} \quad (9)$$

Given two Markov models, we now can define a probabilistic distance between two sequences, denoted by $d(\lambda_1, \lambda_2)$, as

$$d(\lambda_1, \lambda_2) = 1 - \exp[D_s(\lambda_1, \lambda_2)] \quad (10)$$

Figure 2. Phylogenetic tree reconstruction using 3-word composition approach

where D_s is the symmetrized version of the approximate KLD of λ_1 and λ_2 , which is expressed as

$$D_s(\lambda_1, \lambda_2) = \frac{D(\lambda_1, \lambda_2) + D(\lambda_2, \lambda_1)}{2} \quad (11)$$

in which $D(\lambda_1, \lambda_2)$ is the empirical KLD between λ_1 and λ_2 , which was originally introduced by Juang and Rabiner [6] using the Monte Carlo simulations. The models are assumed to be ergodic, having arbitrary observation probability distributions; and the dissimilarity is defined as the mean divergence of the observation sample. This approximate KLD is given by [11]

$$D(\lambda_1, \lambda_2) = \frac{1}{T_2} \log \frac{P(O_{\lambda_2}|\lambda_1)}{P(O_{\lambda_2}|\lambda_2)} \quad (12)$$

where $O_{\lambda_2} = (o_1 o_2 \dots o_{T_2})$ is a sequence of observations generated by model λ_2 , and T_2 is the length of sequence O_{λ_2} .

Finally, the probability of the observation sequence $O = \{o_t, t = 1, \dots, T\}$, given a Markov model λ can be evaluated as

$$\begin{aligned} P(O|\lambda) &= P(o_1, \dots, o_T|\lambda) \\ &= P(o_1) \dots P(o_t|o_{t+1}) \dots P(o_{T-1}|o_T) \\ &= \pi(q'_{t_1}=o_1) \dots a_{q'_{t_n}, q'_{t_{n+1}}} \dots a_{q'_{t_{T-1}}, q'_{t_T}} \end{aligned} \quad (13)$$

3. RESULT

The proposed method was used to reconstruct the phylogenetic tree of 32 complete mammalian mitochondrial DNA genomes. The evolutionary relationship between species as based on sequence analysis of mitochondrial genomes was studied by Reyes *et al.* [12], then Li *et al.* [7], and Otu and Sayood [9].

However, these analyses have led to diverse outcomes and the relative designations remain controversial.

The mtDNA sequences were obtained from the public-domain database of the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov/Entrez/). The genomes consist of members of the primates, rodents, and ferungulates. The primates include human (NC_001807), chimpanzee (NC_001643), pygmy chimpanzee (NC_001644), baboon (NC_001992), gorilla (NC_001645), orangutan (NC_001646), and gibbon (NC_002082). The rodent group includes rat (NC_002083), mouse (NC_005089), dormouse (NC_001892), squirrel (NC_002369), guinea pig (NC_000884), and fruitbat (NC_002009). The ferungulates include cat (NC_001700), dog (NC_002008), harbor seal (NC_001325), gray seal (NC_001602), white rhino (NC_001808), indian rhino (NC_001779), blue whale (NC_001601), finback whale (NC_001321), pig (NC_000845), armadillo (NC_001821), aardvark (NC_002078), elephant (NC_000934), cow (NC_001567), sheep (NC_001941), donkey (NC_001788), horse (NC_001640), hippopotamus (NC_000889), and rabbit (NC_001913). The outgroup consists of platypus (NC_000891).

We used our proposed method to calculate the distance matrix for the above 32 complete mtDNA genomes. For the Markov model, the transition probabilities are of third order where the solution converges. The result plotted by the NJ program in the PHYLIP package [5] is shown in Figure 1. The overall structure of the phylogenetic tree obtained by our proposed approach agrees with those obtained by Reyes *et al.* [12], Li *et al.* [7], and Otu and Sayood [9]. However, the result of the proposed method groups the rodents with the ferungulates; whereas the result obtained by Otu and Sayood groups the primates with the ferungulates.

We also used the word composition approach [16] based on three-word composition statistics to analyze the same data set and the result obtained, which is shown in Figure 2, is similar to that by our proposed method: both methods group the rodents with the ferungulates.

In particular, with the analysis of the rodent group, our method, like the other methods, clusters dormouse with squirrel (nonmurid rodents), and mouse with rat (murid rodents). Our method and the word composition approach do not place the guinea pig, whose position still remains an open question [3], with the two well-supported rodent clades – non-murid rodents and murid rodents. However, the study of mammalian phylogeny is still controversial largely due to conflicting findings regarding the phylogeny of eutherian orders [3, 9].

4. CONCLUSION

We have presented a KLD measure of Markov models for genome phylogenetic tree reconstruction. The experiment on a data set of 32 whole mtDNA genomes has shown the effectiveness of the proposed method. Our proposed method is simple for computer implementation as a new tool for comparative genomics.

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