Parallelized Sequence Comparison of Human and Naked Mole Rat for Aging Studies

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Abstract

A significant increase in the elderly population in the last few decades is expected to rise even more in near future. Inspite of advancement in research on aging; still aging remains unrevealed to a larger extent. Aging is considered to be a major cause for many diseases like cancer, diabetes, Parkinson. The naked mole rat is one of the most promising rodents in aging research. The present work deals with the application of parallel computation to compare the mitochondrial RNA of human with naked mole rat using combined approach of Spectral Clustering and Parallel Markov Models (SCPMM). The clusters obtained using this combined approach appears to be more related to each other than the conventional hierarchical clustering algorithms thus inferring more information from parallel alignment-free sequence comparison. Further studies are being carried out to optimize the code by building a MATLAB-based down-link physical-layer simulator using the parallel computing toolbox and the parallel control flow structure, which significantly reduces the simulation time on multi-core processors.

Keywords: *Aging, Markov Models, Naked Mole Rat, Parallel Computing, Spectral Clustering.*

1. Introduction

Daf-2 was one of the preceding longevity mutant discovered by Kenyon in 1993 in C. elegans [1]. Daf-2 has lead the path for many researchers in the field of aging. Aging is responsible for many complex diseases like diabetes, cancer, Alzheimer and many more. Among the many theories of aging processes, DNA damage theory is the most important one. According to DNA damage theory, aging process is accumulation of naturally occurring DNA alteration. Both mitochondrial and nuclear DNA damage plays a vital role in aging [2]. The production of energy is a basic need in the lifespan of an organism. Most part of the energy is produced in the inner most membrane of mitochondria by complex reactions. Mitochondria contain their own DNA (mtDNA), which is different from nuclear DNA and can be replicated independently of the cell cycle. In support of a role for mtDNA mutations in aging, both mtDNA point mutations and deletions have been described to accumulate on the mitochondrial genome with age in a variety of tissues [3-7]. The age associated accumulation of high level mitochondrial DNA deletions in the dopamine producing pigmented neurons of substantia nigra is additional support for a role of mitochondrial DNA mutations in the aging process. This region of the brain loses neurons and there is an even greater neuronal loss in patients with Parkinson's diseases. mtDNA mutations could be caused by either replication errors or increased oxidative stress[8]. The mitochondrial and oxidation reduction genes in the long-lived naked mole-rat are found to be over-expressed when compared with ordinary mouse [9].

The naked mole-rat (Heterocephalus glaber) also called sand puppy has unique traits which distinguishes itself from other rodents. Some of its unique traits are: it has long lifespan, is a cancer resistant rodent, has substance P deficiency and adaptable to limited oxygen availability [10]. These special characteristics of naked mole rat have further ignited the light in aging research. The mitochondrial genes of three species of human (Denisova hominin, Homo neanderthalensis and Homo sapiens) are compared with naked mole rat using the combined spectral clustering and Markov models. Denisova hominins are paleolithic-era members of a previously unknown species of human or subspecies of Homo sapiens. The Denisova hominins are estimated to have lived 41,000 years ago according to its finger bone analysis. The analysis of the

mitochondrial DNA (mtDNA) of the finger bone showed it to be genetically distinct from the mtDNAs of Homo neanderthals and modern humans (Homo sapiens) [11].

Motivation: Naked mole rats are the longest living rodents with a lifespan of 30 years, which is considered as five times longer than the expected on the basis of body size. Naked mole-rat can be used not only as another model of human biology but mainly as the first model of resistance to diseases like cancer and aging. To analyze the properties, similarity functions and evolutionary homology, DNA sequence comparison between the naked mole-rat and human can be considered. The computational cost involved is more with such alignment-based methods and may not give more findings, which has led the path for discovering alignment-free methods with parallelization.

Contribution: The combined approach SCPMM proposed in this paper is very much interpretable in that, all real sequences are more closely clustered with the new method than the alignment-based hierarchal clustering method. The results from SCPMM are in good agreement with the hierarchal clustering when combined with Markov models. The computational time is considerably minimized with parallelization.

Organization: The remainder of the paper is organized as follows: Section 2 gives description about the related works. Section 3 presents the background and Section 4 describes the proposed method. Section 5 presents the comparative assessment of the proposed method. Concluding remarks are given in Section 6.

2. Related Work

Alberto et al., [12] proposed a method for clustering protein sequences according to their evolutionary relatedness and the cases in which few related proteins have very poor sequence similarity. The local methods fail to cluster protein sequences when they have low similarity measures. Spectral clustering methods are global as they form a cluster by taking into account all the distances between every pair of proteins in the set. They have used BLAST E-values as a distance measure between two sequences.

Tony et al., [13] have proposed a clustering method for time-series data that is embedded with non-parametric spectral clustering with parametric hidden Markov models. This work takes spectral clustering to cluster time-series data. Each time-series is modeled using HMMs. The sequences are grouped according to their pairwise similarity. The work reveals that, spectral clustering with a probability product kernel method results in improved clustering accuracy.

Do et al., [14] have introduced a new scoring function for multiple sequence alignment based on probabilistic consistency. The proposed algorithm ProbCons is a pair-hidden Markov model-based alignment algorithm which is very simple model and needs no background knowledge about gap scoring, tree construction and other features required by other aligners like CLUSTAL W [15]. ProbCons is different from other methods as it uses maximum expected accuracy rather than Viterbi alignment. During pairwise alignment it uses probabilistic consistency transformation to include multiple sequence conservation information.

Weizhong and Adam [16] have discussed Cd-hit on ultrafast protein sequence clustering program. Cd-hit can be applied to many applications. The Cd-hit algorithm is based on short word filtering, which can find out whether the similarity between two bio-sequences is below some threshold value without aligning the sequences. The dipeptides, tripeptides are considered as 'words'. The words that are shared by two proteins are a function of their sequence similarity. If the word count is low the similarity of two bio-sequences is considered as being low, without aligning the sequences. There are wide variety of Cd-hit program called Cd-hit-2d, Cd-hit-est and Cd-hit-est-2d. Cd-hit-est-2d compares two nucleotide sequences.

Searching the genomic and proteomic databases is challenging when the size of the databases are huge. Index based approaches are suitable for such databases. Himanshu and Maulika [17] have discussed a similar method that generates an index of a huge database on 15-residue words. To prepare the index, divide and conquer approach is used. The database is divided into number of segments and index is generated for each segment and finally merged. The algorithm is m times faster as compared to linear search. The algorithm can be adopted for data parallelism.

Shuting et al., [18] have proposed an algorithm that combines the genetic algorithm and a self organizing Neural Network for aligning multiple sequences. They have considered M sequences of various lengths to be aligned. The method proposed achieves improved performance in long DNA and RNA sequences exhibiting slight similarity.

Sequence comparison is an important tool for researchers in molecular biology. Srinivas et al., [19] in their efforts to relate the molecular structure and function to the underlying sequence used prefix computation to derive

parallel algorithms for solving various problems related to sequence comparisons, which reduces the space complexities as well. The proposed parallel sequence comparison algorithm can be used to parallelize other dynamic programming problems. The proposed algorithms are scalable and optimal with respect to time and space.

Vidya A et al., [20] proposed an approach of combined spectral clustering with Markov models to find the similarities between naked mole rat and three human species, which help in aging studies. The computational cost is more due to non-parallelization.

3. Background

In the recent past, quite a good number of computational and statistical techniques have been proposed for sequence comparison in bioinformatics. The most important bioinformatics methodologies for studying the proximity measures of bio-sequences are alignment-based and alignment-free methods. With huge biological databases, the search for optimal solutions using alignment-based method is computationally very expensive, making comparison a difficult task.

Tuan et al., [21] proposed a method for comparing two biological sequences. The method derives a probabilistic distance between the sequences using Kullback-Leibler Divergence (KLD). KLD compares the sequences in terms of Markov models, which is built for corresponding two bio-sequences.

A number of clustering methods have been proposed to group the data objects into classes or clusters. Among them graph based clusters groups the data objects based on the links between the vertices. Spectral clustering is an efficient graph based clustering technique that emerged recently and finds its applications in a wide variety of fields including VLSI design, speech recognition, image processing and in bioinformatics. Spectral clustering is built upon spectral graph theory and uses eigen vectors of a matrix obtained from the distance measures between the objects. Based on the usage of the eigen vectors in slightly different ways, a number of spectral algorithms exists [22].

Parallel Computing Toolbox software allows us to unload the work from one session (client) of MATLAB to other MATLAB sessions (workers). Multiple workers can be used to achieve parallel processing. In addition to parallel MATLAB client session, parallel computing toolbox allows us to run a maximum of eight MATLAB workers on a local machine. The software improves the performance of loop by allowing MATLAB workers to execute individual loops interactions at a time. Parallel-for-loop or parfor loops, is a parallel control flow construct that shares works and executes the body of the loop over a set of available workers [23].

4. Proposed Model

4.1 Problem Definition

Given the biological sequences of different species, the objectives are:

(i) To compare alignment-free and alignment-based sequence comparison methods.

(ii) To optimize the computational time required to compare sequences.

4.2 System Model and Design

The proposed model for sequence comparison of different species is as shown in Fig. 1.

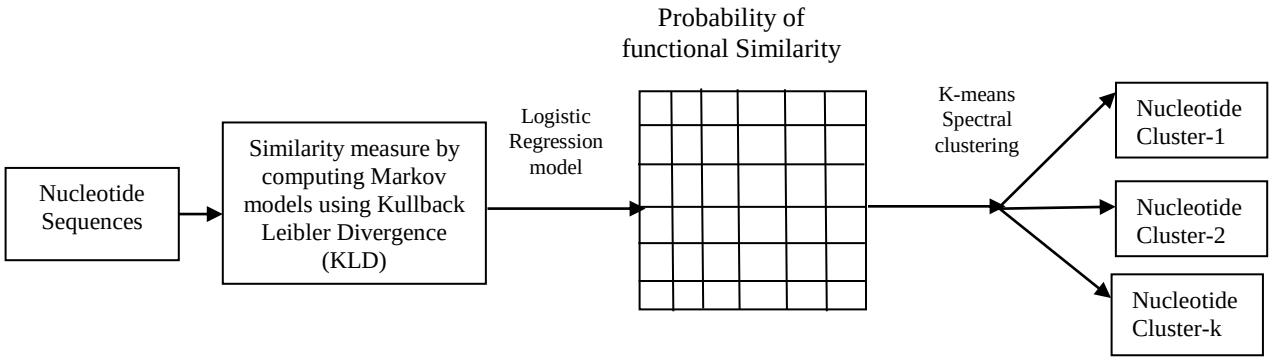

Fig. 1 The Proposed Model for Sequence Comparison of Different Species.

4.2.1 Dataset

We focused our study on the mitochondrial RNA of human and naked mole rat. All the sequences of naked mole rat and mitochondrial genome sequences of three human species are retrieved from NCBI database [24]. (Homo Sapiens (HS); Homo Neanderthalensis (HSN); Denisova hominin (HSA); Naked Mole Rat (HG)). The 13 mitochondrial sequences are ATP8, ATP6, ND1, ND2, ND3, ND4, ND5, ND6, COX1, COX2, COX3, CYTB, and ND4L.

4.2.2 Methodology

The FASTA format of these sequences is given as an input to Markov models. The probability similarity matrix of these sequences is obtained by comparing Markov models. According to Tuan et al., [21], Let A = $[a_{ij}]$ be a state transition probability matrix of a discrete Markov model. Where, a_{ij} denotes the individual state transition probability and is given by Eq. (1).

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

q_{tn} is actual state at time t_n (n = 1, 2, . . .), S is a set of N distinct states. In the perspective of DNA sequences, the number of states N corresponds to the four nucleotide symbols {a, c, g, t}. The state transition probabilities subject to the constraints are given in Eq. (2) and Eq. (3).

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

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

Let, $\pi = \{\pi_i\}$ be the initial state transition distribution, represented by Eq. (4).

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

The Markov chain involves two probabilistic measures A and π, denoted in a solid form as in Eq. (5)

$$\lambda = (A, \pi). \qquad (5)$$

The above model is called the first order Markov model. We can also define second, third and higher order Markov models, but our process is based only on the first order Markov model. Let $\lambda_1 = (A_1, \pi_1)$ and $\lambda_2 = (A_2, \pi_2)$ be two Markov model of first order of the two bio-sequences, where each model is constructed by the observed symbols of each corresponding DNA sequence. Our objective is to find a similarity or dissimilarity measure between two Markov models λ_1 and λ_2. A well-known dissimilarity measure between two probability distributions called Kullback–Leibler Divergence (KLD) is used.

We apply spectral clustering technique to our nucleotide sequences of human and naked mole rat. The spectral clustering forms the clusters of sequences by partitioning a graph into a set of discrete clusters. Each vertex of the graph corresponds to a sequence and the cost on each edge represents the similarity between the two sequences. We are interested in regions in the graph, in which the vertices are connected by highly similar edges and the connections between such regions should be weak, comprising of edges with low similarity. The objective is to identify strongly connected clusters and cut the inter cluster edges. The spectral clustering methods are global and produce results better than some local methods [12].

4.2.2 Algorithm

In the proposed approach of combined Spectral Clustering with Parallel Markov Models is to replace the affinity matrix in the spectral clustering algorithm proposed by Andrew et al., [22] with the probability similarity matrix measure by comparing Markov models using Kullback-Leibler Divergence (KLD). The modified algorithm Spectral Clustering with Parallel Markov Models (SCPMM) is as follows:

1. Computation of probability matrix *P* of sequences by comparing Markov Models [21].
2. Construct the Laplacian matrix *L*, with the help of diagonal matrix *D* of matrix *P*.
3. Form the matrix $E=[e_1,e_2,\ldots,e_k]$ of first *k* eigen vectors of *L*.
4. Compute the normalized matrix *Z*, such that each of *E*'s rows in *E* has unit length.
5. Apply k-means clustering algorithm to cluster each row of *Z* into *k* clusters.
6. Assign the original point to cluster *j* if and only if row *i* of the matrix *Z* was assigned to cluster *j*.
7. End.

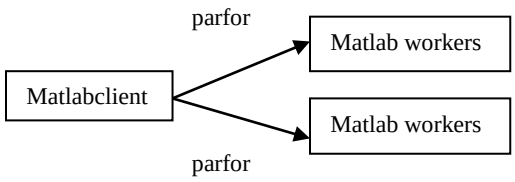

Fig.2 Parallel Computing Using Matlab Parallel Computing Toolbox

The program is executed using Intel Core i3 CPU Multi-core Processor with 2.53GHz clock speed with 8GB RAM. Two MATLAB workers were given using matlabpool command and all for loops were converted into parfor loop for implementation of parallel computing [23]. Fig. 2 depicts the parallel computing using MATLAB Parallel Computing Toolbox. The parallel computation was performed by annotating all for loops present in the Markov Model program to parfor. There are five steps in the execution of a parfor loop:

1. Initialize the resources executing the matlabpool command
2. A static analysis of the loop
3. Transfer the code and data to the compute resources.
4. Execute the code initiated on workers
5. Combine the results from the compute resources.

5. Results and Discussions

The results obtained from hierarchical and spectral clustering are as shown in Fig. 3, Fig. 4 and in Table 1 respectively. In Hierarchical clustering, there are 13 branches (branch 37, 29, 31, 34, 30, 27, 35, 28, 32, 38, 33, 36 and branch 39) which shows 13 different mitochondrial sequences. The results from the hierarchical clustering clearly states that the naked mole rat (HG - prefix) sequence is separated from the three Homo sapien species (Fig. 3) leading to difficulties in analyzing the similarities between the sequences.

Hierarchal clustering results using the Markov Model algorithm is also plotted as in Fig. 4. All the trees are drawn to an equivalent overall size. It can be observed that on a relative scale, all the real sequences appear to be less related to each other in the Hierarchal clustering algorithm than in the tree using the Hierarchal clustering algorithm with Markov Model. In other words, all real sequences are more closely clustered with alignment-free method than the alignment-based Hierarchal clustering method.

The spectral clustering results are shown in Table 1. The 13 clusters that are used is based on the 13 different mitochondrial dataset which is taken from all four species (Naked mole rat, Homo sapien, Homo Neanderthalensis and Denisova hominin). In spectral clustering with K-means, the similarities are found in the sequences in cluster 10, cluster 8 and cluster 3. Further experimentation can be done for finding the exact similarities of the species. Three sequences of naked mole rat are clustered in the cluster 10 along with ND1 sequence of Homo sapien, Homo Neanderthalensis and Denisova hominin leading to importance of the cluster 10 sequences.

Table 1: K-mean Clustering Results from the Algorithm.

Cluster No.	Sequences	Cluster No.	Sequences	Cluster No.	Sequences
1	HSAATP6	5	HSND6	9	HGCOX3
1	HSND3	5	HGND6	10	HSAND1
1	HSATP6	5	HSNND6	10	HSND1
1	HSNND3	6	HSAND5	10	HGND3
1	HSNATP6	6	HSAND3	10	HGND5
2	HSAND2	6	HSND5	10	HGATP8
2	HSND2	6	HSNND5	10	HSNND1
2	HSNND2	7	HGND4	11	HSACOX3
3	HSACOX2	7	HGCOX2	11	HSCYTB
3	HSCOX2	7	HGCYTB	11	HSNCOX3
3	HGND2	8	HSAND4L	11	HSNCYTB
3	HSNCOX2	8	HSND4L	12	HGND1
4	HSACOX1	8	HSATP8	12	HGND4L
4	HSAATP8	8	HGCOX1	13	HSAND4
4	HSCOI	8	HGATP6	13	HSND4
4	HSNCOX1	8	HSNND4L	13	HSNND4
4	HSNATP8	9	HSACYTB	–	–
5	HSAND6	9	HSCOX3	–	–

Table 2: Program Execution Time With and Without Parallelization.

Program Execution Time (in seconds)	
Markov Model without Parallelization	Markov Model With Parallelization
2.540944	2.024409

The spectral clustering results are same as the hierarchal clustering algorithm with Markov model in distinguishing sequence from a group of related natural sequences as a whole. Table 2 records the time required to execute the program with and without parallelization. It clearly shows that the execution time can be optimized by adopting parallelization.

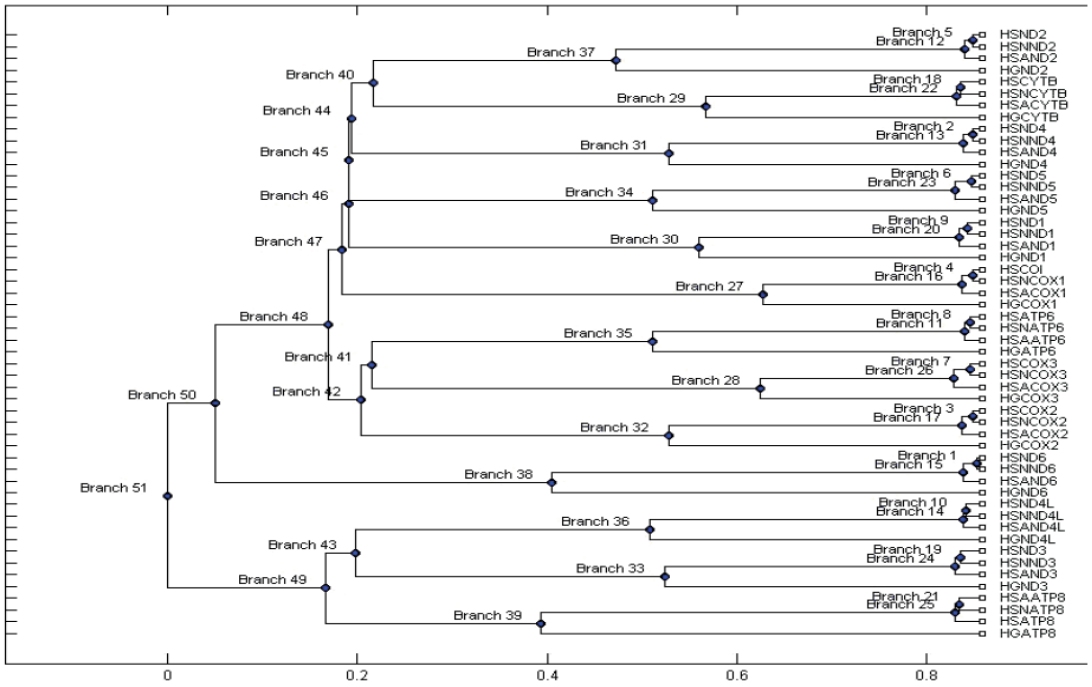

Fig. 3 Hierarchical Clustering (alignment-based) of Naked Mole Rat and Homo Sapien Species Sequences.

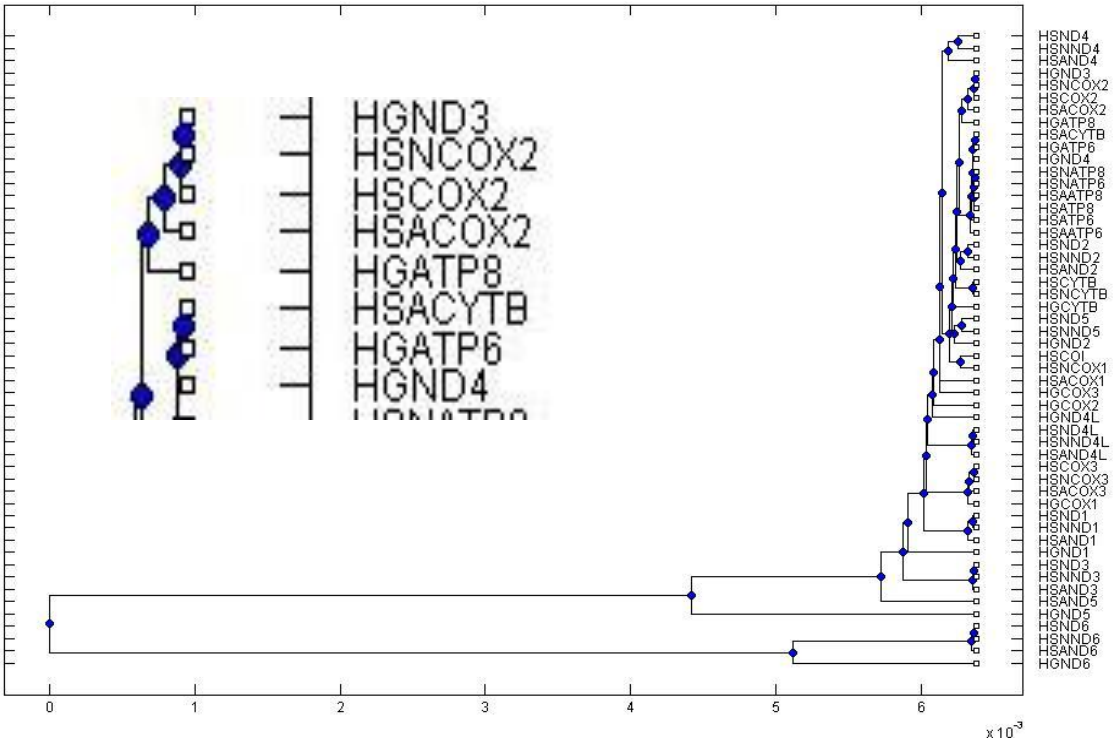

Fig. 4 Hierarchical Clustering (alignment-free) of Naked Mole Rat and Homo Sapien Species Sequences

6. Conclusions

To analyze the properties, similarity functions and evolutionary homology DNA sequence comparison between the two sequences is considered as an important step. Such analysis is done by alignment-based comparison. An alignment-free comparison method is introduced into the spectral clustering algorithm. The Kullback-Leibler Divergence is first applied in this spectral clustering algorithm for finding the similarities of mitochondrial sequence of naked mole rat with three different species of human beings. The similarities suggest that ND1 sequence of all three species of human being is found to cluster with three mitochondrial sequences of naked mole rat leading to new findings in the aging research. An alignment-free Markov Model algorithm with spectral clustering (K-means) is found to be superior when compared with the hierarchal clustering (CLUSTAL W). The execution time was significantly optimized and it is proved that the proposed methodology can be further explored to parallelize and compute the clustering of larger sequence datasets.

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