Application of Ant Colony Optimization in Identifying the Key Gene Interactions

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Abstract: Optimization is necessary to ensure the quality of data and to strengthen the validity of standardized results in making decision. Diverse research works on meta-heuristic for optimization is recently becoming popular among researchers. Various optimization techniques can be applied to extract and explore meaningful information from high dimensional dataset. In this paper, Ant Colony Optimization (ACO) method is used to optimize the gene similarity network path and forming functional clusters of genes from a semantic similarity graph derived using Gene ontology. The results are promising when compared with the standard benchmark community detection algorithm.

Keywords: Ant Colony Optimization, Clustering, Gene Ontology, Semantic Similarity, Optimum path.

1. INTRODUCTION

Genetic interaction network (GIN) plays an important role in identifying the functional relationships of genes. In GIN, genes are connected together as a network where the nodes of each network will correspond to a gene or physical elements like protein, RNA, metabolites and each edges represents the relationship between these elements. In a genetic network, genes are not independent but they regulate each other and act collectively.

Data mining is one of the inter-disciplinary fields, whose goal is to extract knowledge from data. The diversity of knowledge and data mining functionalities are categorized as characterization, association analysis, clustering, classification, discrimination, prediction, outlier analysis, evolution and deviation analysis.

Classification is related to the natural decision making of humans. The classification is a problem of identifying and learning problem where training set of correctly analysed remarks are available [19,20]. Some of the classification techniques are Naïve Bayesian, Decision tree, k-nearest neighbor classifiers, neural networks, and support vector machines (SVMs)[1]. Supervised learning methods can be employed if the training sets of data with class labels are available.

Clustering is a way of treating similar objects into a single group[21,22]. The cluster analysis is being processed by partitioning the data into groups based on data similarity and assigning labels to each group. The wide variety of applications based on cluster analysis has been introduced such as image processing, market research and data analysis. In certain biological datasets, unsupervised learning methods are most commonly used since the class labels are missing or not labelled for most of the time[2,3]. By applying clustering, genes are categorized into similar functional groups which share common characteristics.

Optimization is the act of obtaining best solution from a set of constraints. In 1992, Marco Dorigo introduced Ant Colony Optimization (ACO)[4,5,26]. ACO algorithm initiates meta-heuristics optimization based on Swarm
Intelligence to obtain excellent solution from a set of parameters[6]. The Ant System is the first ACO algorithm applied in Travelling Salesman Problem (TSP)[7]. ACO is used to maximize or minimize a set of parameters in a function. Here, the goal is to maximize the accuracy of gene interaction network path where the function is defined as

\[ f(x) = \max(\text{gene similarity network path}) \]

The approach of ACO is from the foraging behaviour of real ants to find the optimal path between their nest and food source. To enable ants to find the shortest path an indirect communication is made using a chemical pheromone trail. In nature, an ant is a single individual which moves randomly to find a source of food and a chemical substance deposited on the ground by ants is known as pheromone. Figure 1 shows how ant randomly moves to find a source of food and obtaining a best path.

![Fig. 1. Natural Behaviour of Ants.](image)

The Gene Ontology (GO) is an authorized standard that holds the structured and controlled biological terms maintaining the consistency in describing the functional relationship among different gene functions. Nowadays, GO is widely used as an annotation system to determine the importance of biological experiments. The principle is based on the concept that if more than two genes are associated by an experiment, they should be associated by known gene function. Basically, GO comprises of three root ontologies cellular component, biological process and molecular function. Cellular component explains the sections of larger structure and gene product groups. A biological process illustrates a sequence of events consisting of various sets of molecular functions. Molecular function represents the activities that occur at molecular level rather than the complexes that never specify where the action takes place. These three ontologies are structured in the form of a directed acyclic graph (DAG) such that each node represents a parent-child relationship.

The paper is formatted as follows: Section 2 summarizes the related works. Section 3 demonstrates proposed system and Section 4 shows the experiments and results of proposed model and Section 5 concludes with remarks.

2. RELATED WORKS

Various ACO schemes has been proposed to find the shortest possible path based on Travelling Salesman Problem(TSP)[8,9,24]. The first ACO algorithm has been proposed by Thomas Stutzle and Mark Dorigo called Ant System has been applied to TSP. Later, several improvements on Ant system were proposed on the basic algorithm. By using local search algorithms, performance of ACO algorithms for TSP helped to enhance the solutions generated by ants.[18,23]

In the field of machine learning, diverse problems have been tackled by means of ACO algorithms. ACO is adapted for learning the structure of Bayesian networks by De Campos[10]. Later training of neural networks by means of ACO was developed by Socha and Blum which is an application of ACO to continuous problems.[11]

Later, A.E Rizzoli proposed a Vehicle Routing Problem (VRP) that can handle with the transportation of items between warehouse and customers by means of group of vehicles.[12] The VRP focuses on finding the best route using fleets of vehicles, observing all operational constraints, such as vehicle capacity and the driver's maximum working time, and minimizing the total transportation cost and serving all customers. However, the most typical goal is to minimize the transportation costs based on the function of the travelled distance or time; the number of vehicles can be minimized expelling the costs associated with vehicles and drivers.
Recently, a problem on Water Distribution System (WDS)[25] was proposed by Aaron C Zecchin and Angus R Simpson which was the best application of ACO in Natural Computing (Computational Intelligence) Methods to Water resources and Environmental Modeling[13]. WDS use ACO to minimize the design costs of the infrastructure. Selecting the lowest cost combination of appropriate component, diameter sizes and selection of valve pressure, location of valve and pump settings provide WDS as satisfied. It uses the max-min ant system algorithm to search around the best solution found in each iteration. The pipes or pumps are associated with the decision variables within the system.

Decision trees have been used with ACO algorithms to improve the accuracy of decision tree. For this, Ant Miner is the efficient way to discover classification rules using ACO. There are various decision tree induction algorithms available such as C4.5, CART and cACDT, in 22 publicly available data sets. The cACDT is ACO based decision tree algorithm.[14]

In contrast to the approach proposed by Khalid Raza and Mahish Kohli[15], which is based on the gene interaction using ACO from gene expression, which tend to help in identifying bookmarks of diseases found in genes.

Here, we explored the application of ant colony optimization in extracting the key gene interactions from gene network. The proposed approach is an integrated ACO based clustering solution for finding groups of functionally similar genes.

3. PROPOSED SYSTEM

The perspective of proposed system explains how ACO is applied in semantic similarity matrix for obtaining a gene similarity network path for a large complex biological dataset by finding genes which has high density of pheromone. The process flow of the proposed approach is depicted in Figure 2. Different steps involved in the process are given below:

**Step 1**: Create Semantic Similarity matrix

**Step 2**: Optimum semantic network path identification using Ant Colony Optimization.

**Step 3**: Gene Clustering from the optimum path.

![Fig. 2. Process flow of gene clustering using ACO.](image)
PSEUDO CODE OF THE PROPOSED APPROACH

Table 1 illustrates the parameters used in the algorithm and Table 2 describes the step by step procedure in applying ACO in semantic similarity matrix for obtaining meaningful clusters.

Table 1. Initializing basic parameters

Let N represent number of genes.
R represent N*N matrix that represents the semantic similarity measure of genes using Resnik formula (Equation 3).
S1,...,k represents the solution space that k solutions of the form gene similarity network path (eg: g1-g3-g5,......gN).
Local\textsubscript{best} represents the local optimum value of each solution.
Global\textsubscript{best} represents the global optimum value.
Global\textsubscript{path} represents the gene similarity network path that returns the global optimum solution.
P represents the Pheromone matrix N*N.

Table 2. Description of the proposed ACO-based clustering algorithm.

\[ F(x) = \text{maximum gene similarity network path} \]

1. Place all ants at different genes randomly in the semantic similarity matrix, R.
2. Create k solutions forming different gene similarity paths based on random movements of ants by setting the condition that the ant should visit all gene nodes at least once.
3. Find the local optimum value of each solution by computing the sum of similarity index of all edges of each gene network path
   \[ \text{Localbest}(1...k) = \sum_{i=1}^{N} (g_{ij}) \]
4. Compute Global\textsubscript{best} solutions as Max ( Local\textsubscript{best}(1...k)) and Global\textsubscript{path} as the gene similarity network path that return the global optimum solution.
5. Create a Pheromone matrix by recoding the Global\textsubscript{best} value for all edges corresponding to the Global\textsubscript{path} in the matrix.
6. For next iterations, ants are taking route based on the optimum value in pheromone matrix, P.
7. The Pheromone matrix will be always updated with the optimum value i.e. if the existing matrix value <Global\textsubscript{best} value , replace with the new value.
8. Repeat the process till the number of iterations is completed.

Step 1: Create Semantic Similarity Matrix : Usually GO annotations are used to define the functional relatedness by using “semantic similarity”[16]. Semantic similarity is a process used to measure the resemblance of concepts belonging to ontology. Generally, the semantic similarity is evaluated based on distance between the nodes such that the nodes having shortest path indicates more similar they are [15,17]. Recently, the semantic similarity measure for molecular function is becoming popular among researchers. Molecular function describes the biochemical activities at the molecular level and it is a convenient way to study gene functional similarity by comparing terms which support wide variety of applications. Hence, in this paper we use molecular function for analysis.

The semantic similarity measure used in this paper is based on information content of each term. The similarity measures is derived either from the GO term information content(IC), a numerical value depicting the description of a GO term using the position in the GO DAG or from GO term semantic similarity measurement depicting the information shared by two GO terms in GO DAG. IC is based on factors like, the frequencies of two GO terms involved and closest common among ancestor term in GO annotation and GO term is calculated by negative log probability of the term. The frequency of a term t can be calculated as
\[ p(t) = \frac{n_t}{N}, \quad t' \notin \{ \text{children of } t \} \]  

(1)

where, \( n_t \) is the number of term \( t \), \( N \) is the total number of terms in GO corpus.

The information content can be calculated using:

\[ \text{IC}(t) = -\log(p(t)) \]  

(2)

where, \( p(t) \) is the frequency of GO term \( t \).

Multiple parents for each concept is allowed in GO such that, two terms can share parents by multiple paths. In IC based method, similarity of two GO terms can be calculated based on common closest ancestor term of the information content which is referred to as most informative information ancestor (MICA).

Typically, there are four metrics based on information content proposed by Resnik, Jiang, Lin, and Schlicker.

**Resnik method**: To compute the similarity Resnik Philip proposed a method defined as:

\[ \text{sim}_{\text{Resnik}}(t_1, t_2) = \text{IC}(\text{MICA}) \]  

(3)

where \( t_1, t_2 \) are GO terms, \( \text{IC}(\text{MICA}) \) represents information content of common closest ancestor terms.

**Lin method**: The Lin method was proposed by Dekang Lin. The method is defined as:

\[ \text{sim}_{\text{Lin}}(t_1, t_2) = \frac{2IC(\text{MICA})}{IC(t_1) + IC(t_2)} \]  

(4)

where the \( IC(t_1) \) and \( IC(t_2) \) are the information content of GO terms \( t_1 \) and \( t_2 \) respectively.

**Rel method**: The Relevance method proposed by Schlicker is the combination of both Resnik’s and Lin’s method. The Rel method is defined as:

\[ \text{sim}_{\text{Rel}}(t_1, t_2) = \frac{2IC(\text{MICA})(1 - p(\text{MICA}))}{IC(t_1) + IC(t_2)} \]  

(5)

**Jiang method**: Jay J. Jiang and David W. Conrath proposed a method using the information from both text corpus and conceptual taxonomy to find semantic similarity. The method is defined as:

\[ \text{sim}_{\text{Jiang}}(t_1, t_2) = 1 - \min(1, \text{IC}(t_1) + \text{IC}(t_2) - 2\text{IC}(\text{MICA})) \]  

(6)

We are using Resnik measure to find the correlation between genes from a set of genes and a semantic similarity matrix is generated for further analysis.

**Step 2**: Optimum semantic network path identification using Ant Colony Optimization

To generate an optimum path, Ant colony optimization technique is applied and similarities among the key gene interactions can be found. The Ant Colony Optimization for finding the functional similarities of genes is illustrated using the following steps:

**Initialization**: During initialization of algorithm, variables are initialized and parameters are set. Now randomly place all ants at different locations of genes in semantic similarity matrix \((N*N)\) for movements and forming paths.

**Movement**: The ant moves randomly covering all the genes and thus generating solutions of gene similarity paths. The movement of ant is based on the condition that it should visit all gene nodes at least once. Each path is been recorded in a solution set. From each solution a local optimum value is computed by finding the sum of cell entries of all edges of gene network path. Again, a global optimum value is being computed by finding the maximum values among local optimum value of each solution. A global path corresponding to the global optimum value has been considered as optimum gene network path.

**Pheromone Update**: A pheromone matrix \((N*N)\) is been created to record these global optimum value, corresponding to the global path for all the edges. The pheromone matrix is being referred for the next iteration of ant to select their route. The pheromone matrix is always being updated with optimum values such that, if the matrix value is less than the global optimum value, then replace it with the new value. The process is being repeated till number of iterations is completed.
**Step 3: Gene Clustering from the optimum path**: After completing all the iterations, the pheromone matrix will be updated with the optimum semantic similarity values of gene to gene interactions. Hence, the gene movements are converged to the global optimum solution. From the optimum similarity path, clusters are formed based on the functional similarities of genes by breaking the paths which shows huge variation in the similarity values.

**4. EXPERIMENTS AND RESULTS**

To implement the proposed system, a cancer gene list is being adopted from Illumina Inc., a Biotechnology company which focuses on the development of analysis of genetic variation and biological function. The target cancer gene list is available online which enables researchers to access and analyse the variation among genes. The cancer gene list consists of 92 genes that have been identified from the study of cancer. These genes are associated with most common cancers such as colon, breast cancer and some of the rare cancers.

In order to find the semantic similarity between genes, an information content based Resnik method is being adopted. The result obtained here is in the form of similarity matrix representing the genes in the form of rows and columns. Each cell entry is based on semantic similarity measurement based on Gene Ontology programming and the packages associated with it is being selected for the implementation purpose. 10 meaningful clusters were formed using the proposed algorithm. To validate the approach, we used k-means clustering and measured the cluster-betweeness value by setting k value from 3 to 15. Figure 3 shows the trend chart showing the cluster separation value for different cluster sizes. If we plot k against the BSS, we can see the value increases as k gets larger; reaching an optimum value and then start decreasing. Ideal cluster size is to choose the k at which the BSS shows maximum value. Here the optimum cluster size is showing as 10 which is same as the cluster size generated automatically using the proposed approach.

![Cluster-Betweenness](image)

**Fig. 3. Cluster-betweeness for different cluster size in k-means.**

From each cluster, gene features are being extracted using MeSH terms to validate the feature similarity among genes. Table 3 listed the clusters with common functionalities. The existing approach is also compared with community detection algorithm, walk trap where only two clusters were formed, which is depicted in Table 2. To explore the common characteristics of genes and to identify gene interactions that contribute for common phenotypes or disease type, the new approach is useful.
### Table 3: Common functionalities of genes in Cluster

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Gene Names</th>
<th>Common functionalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>KIT, ALK, EGFR, MET, TP53, DDB2, ERCC3, RECQL4, BLM, WRN, MEN1, MSH2, MSH6, PMS2, MLH1, MUTYH</td>
<td>Receptor Protein-Tyrosine Kinases, Phosphorylation, Prognosis, Antineoplastic Agents, Stem Cell Factor, Immunohistochemistry.</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>APC, CDH1</td>
<td>Adenocarcinoma, Desmplakins, +HT29 Cells, Adenomatous Polyposis Coli Protein, Trans-Activators, Aged.</td>
</tr>
<tr>
<td>Cluster 3</td>
<td>BRCA1, NSD1, RB1, EZH2, SMARC B1, CDKN2A, CDK4, PTCH1, NF1, TS C2, TSC1, ATM, ERCC2, BRIP1, NBN, ERCC4, FANCG, XPA, XPC, ERCC5, RAD51C, SLX4, DICER1, DIS3L2, ST K11, PRKAR1A, CHEK2, FANCL, VHL, AIP, CEBPA, MAX, SUFU, CYLD, BAP1, FANCM, GATA2, WT1, HNF1A, PHOX2B, SMAD4, BMPR1A, CEP57</td>
<td>DNA-Binding Proteins, Germ-Line Mutation, DNA Repair, Ubiquitination, Tumor Suppressor Proteins.</td>
</tr>
<tr>
<td>Cluster 4</td>
<td>EXT1, EXT2</td>
<td>C4, Trans-Activators, Transcription Factors, Transforming Growth Factor beta, Signal Transduction, Protein-Serine-Threonine Kinases.</td>
</tr>
<tr>
<td>Cluster 5</td>
<td>RUNX1, P RET, RF1, BUB1B</td>
<td>Heparitin Sulfate, Proteins, N-Acetyl Hexosaminyl transferases, Bone Development, Glycosyl transferases, Bone Neoplasms.</td>
</tr>
<tr>
<td>Cluster 6</td>
<td>BRCA2, RAD51D, PMS1, PALB2, SBDS, CDC73, EPCAM, FLCN, PTEN</td>
<td>Mutation, Tumor Suppressor, Proteins, DNA Mutational Analysis, Germ-Line Mutation, Carcinoma, Loss of Heterozygosity, DNA Repair.</td>
</tr>
<tr>
<td>Cluster 7</td>
<td>FANCD2, FANCI</td>
<td>HeLa Cells, Proteomics, Lysine, BRCA2 Protein, Ubiquitinated Proteins, Cell Line.</td>
</tr>
<tr>
<td>Cluster 8</td>
<td>TMEM127, CDKN1C, FANCA, FANCB, FANCC, FANCF, FH</td>
<td>Fanconi Anemia, Fanconi Anemia Complementation Group L, Protein, DNA Helicases, BRCA2 Protein, Fanconi Anemia Complementation Group Proteins, Cell Cycle Proteins.</td>
</tr>
<tr>
<td>Cluster 9</td>
<td>SDHD, SDHB</td>
<td>Young Adult, Proto-Oncogene Proteins, c-ret, Paraganglioma, Abdominal Neoplasms, Head and Neck Neoplasms, Adolescent.</td>
</tr>
<tr>
<td>Cluster 10</td>
<td>GPC3, HRAS, SDHC, NF2, SDHAF2</td>
<td>DNA Mutational Analysis, Abnormalities, Multiple, Succinate Dehydrogenase, Polymorphism, Single-Stranded Conformational, Cell Proliferation, Mosaicism.</td>
</tr>
</tbody>
</table>
Table 4. Results of walk trap community detection algorithm (only 2 clusters formed)

<table>
<thead>
<tr>
<th>Clusters</th>
<th>Gene Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1</td>
<td>AIP, ALK, APC, ATM, BMPR1A, BMPR1A, BUB1B, CDC73, CDH1, CDK4, CDKN1C, CDKN2A, CEBPA, CEP57, CHEK2, CYLD, EGFR, EPCAM, EXT1, EXT2, FANCA, FANCB, FANCC, FANCD2, FANCF, FANCI, FANCL, FANCM, FH, FLCN, GPC3, KIT, MAX, MET, MUTYH, NF1, NF2, NSD1, PRF1, PRKARIA, PTC1, PTEN, RBI, RET, SDHAF2, SLX1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL</td>
</tr>
<tr>
<td>Cluster 2</td>
<td>BAP1, BLM, BRCA2, BRIP1, DDB2, DICER1, DIS3L2, ERCC2, ERCC3, ERCC4, ERCC5, EZH2, FANCG, GATA2, HNF1A, HRAS, MEN1, MLH1, MSH2, MSH6, NBN, PALB2, PHOX2B, PMS1, PMS2, RAD51C, RAD51D, RECQL4, RUNX1, SBDS, SDHB, SDHC, SDHD, SMAD4, SMARCBI, WRN, WT1, XPA, XPC</td>
</tr>
</tbody>
</table>

5. CONCLUSION

Gene clustering is used for exploring homogeneous groups of functionally similar genes that contribute for same phenotype or disease type. We have integrated ant colony optimization technique in clustering to extract highly connected gene network path from the set of genes and forming meaningful functional groups of genes. The approach is validated using cancer data set and the clusters shows common functionalities when reviewed with existing biological data sources. We have compared the existing approach with walk trap community detection algorithm and the results shows that the proposed approach gives more optimized and accurate results. The future work is to implement the same solution in other domains and for large datasets.

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7. REFERENCES

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