Efficient Determination of Biological Relatedness

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Abstract

Determining the biological relatedness of disease-associated genes often relies on the Average Shortest Path Length (ASPL) in protein-protein interaction (PPI) networks. Typically, the ASPL of disease genes is compared to randomly selected genes or networks to identify significant patterns of connectivity. However, computing shortest paths in dense biological networks using algorithms like Dijkstra's is computationally expensive, and storing all-pairs shortest paths scales quadratically, making real-time analysis infeasible.

To address this, we propose an efficient data structure which can cache these distances. We approximate the shortest paths with reduced storage complexity. In our approach, we use a structure that approximates the distance between gene pairs with an additive error of at most (2d + 1), where 'd' is the true shortest path distance.

This approximate representation significantly reduces the storage requirements while preserving sufficient accuracy for ASPL computations. The small additive error ensures that the approximated distances still reliably reflect the biological relatedness of disease-associated genes.

By using this optimized structure, we achieve efficient real-time querying of shortest path distances, overcoming the computational bottleneck and storage explosion of traditional approaches. This enables scalable analysis of disease gene networks and paves the way for deeper insights into biological connectivity patterns.

1 Introduction

Works by Embar et. al [1] show that the shortest path length between genes in a protein-protein interaction (PPI) network can be regarded as a crucial metric for determining their biological relatedness. In biological networks, genes associated with a common disease or pathway often exhibit closer interactions, and their protein products tend to form tightly connected clusters. The Average Shortest Path Length (ASPL) is commonly used to quantify this phenomenon, comparing the connectivity of disease-associated genes with randomly selected gene sets. Research has shown that genes with shorter ASPLs often share functional or biological relationships, making this metric invaluable in understanding disease mechanisms, gene prioritization, and pathway analysis. However, it has also been noted that the ASPL is influenced by the degree distribution of genes within the network, emphasizing the need for careful analysis and interpretation.

While shortest path analysis offers valuable insights, it presents significant computational and storage challenges. Computing shortest paths across large, dense biological networks using algorithms like Dijkstra's can be computationally expensive, especially when real-time querying is required. Furthermore, precomputing and storing all-pairs shortest paths scale quadratically with the number of genes in the network, leading to prohibitive memory requirements. Traditional data structures, such as hash tables, struggle to manage this scale efficiently, resulting in slow query times and impractical storage demands. To tackle this problem we can try approximations but existing approximation tools can only provide answers upto 3x errors which is not suitable for biological classification. So we try to design an algorithm that can provide below 3x error for better suitability

To address these challenges, we test and use an efficient data structure to see if we can come up with an algorithm with feasible time and space complexity that can determine the biological relatedness in as less time and compute as possible. Our approach approximates shortest path distances with a minimal additive error of (2d + 1). This approximation significantly reduces storage requirements while enabling real-time querying of distances between gene pairs. By using this optimized structure, we overcome the computational and storage bottlenecks of traditional shortest path algorithms, making it feasible to analyze large-scale biological networks efficiently.

2 Methodology

In this section, we outline the methodology used to construct an efficient data structure for approximating shortest path distances in large-scale protein-protein interaction (PPI) networks. The primary goal is to address the computational bottleneck and storage challenges associated with determining biological relatedness through the Average Shortest Path Length (ASPL). We utilize a two-level sampling approach that enables scalable and real-time querying of distances between gene pairs.

2.1 Construction of the Data Structure

Our approach begins with the construction of an efficient data structure that leverages landmark-based sampling and neighborhood sampling. The two-level sampling strategy enables us to store only a subset of the shortest paths, thus reducing both space and time complexities.

2.1.1 First Level: Sampling Landmarks

The first level of our construction involves sampling a subset of vertices, referred to as landmarks, from the PPI network. Each vertex is independently sampled with a probability of $p_1 = n^{-1/3}$, where n is the total number of vertices in the network (genes in this case). The expected number of sampled vertices is given by:

$$E[|A|] = n \cdot p_1 = n \cdot n^{-1/3} = n^{2/3}.$$

These landmarks serve as reference points for approximating shortest path distances in the network. The idea is that, by sampling a subset of vertices, we can efficiently approximate the shortest path between any two vertices by considering their proximity to the sampled landmarks.

2.1.2 Second Level: Neighborhood Sampling

In the second level, we perform additional sampling within the neighborhood of the sampled landmarks. Each vertex is independently sampled with a probability of $p_2 = n^{-2/3}$. The expected number of sampled vertices in this step is:

$$E[|B|] = n \cdot p_2 = n \cdot n^{-2/3} = n^{1/3}.$$

For each sampled vertex $u \in B$, we define a neighborhood ball, $Ball_A(B)$, as the set of vertices within a certain distance from the nearest landmark in set

A. Mathematically, the ball is defined as:

$$Ball_A(B) = \{v \mid d(u, v) < d(u, A)\},$$

where $d(u, A)$ represents the shortest distance from vertex u to any vertex in the landmark set A. The expected size of this ball is bounded by:

$$E[|Ball_A(B)|] \leq n^{1/3}.$$

This sampling process helps in identifying local regions of the network that are likely to contain significant interactions, allowing for more efficient distance queries.

2.1.3 Expected Size of the Data Structure

The expected total size of the data structure, denoted by set C, is the union of the landmark set A and all the neighborhood balls $Ball_A(B)$ for each vertex $u \in B$. The total expected size is computed as:

$$E[|C|] \leq E[|A|] + \sum_{u \in B} E[|Ball_A(B)|] \leq n^{2/3} + n^{1/3} \cdot n^{1/3} = 2n^{2/3}.$$

Thus, the data structure is significantly smaller than the full all-pairs shortest path matrix, which would scale quadratically with the number of vertices in the network.

2.2 Querying the Distance

When a query (s, t) arrives, the algorithm proceeds to approximate or compute the shortest path distance between the gene pair s and t using the following steps:

1. **Same Neighborhood:** If both s and t are found in the same neighborhood ball $Ball_A(B)$, the exact precomputed distance between them is returned.

2. **Neighborhood Intersection:** If the neighborhoods of s and t intersect, the exact distance is retrieved from a precomputed hash table.

3. **Approximation:** If neither of the above conditions hold, the distance is approximated by using the nearest landmarks of s and t in set A. This approximation introduces a small additive error of at most $2d+1$, where d is the true shortest path distance.

This approach ensures that the majority of queries are answered in constant time, while only a small fraction of the queries may require approximation with a small error margin.

2.3 Pseudocode

Construction Algorithm:

Algorithm 1 Construction of Distance Oracle

1: Sample vertices into sets A and B with probabilities p_1 and p_2, respectively.
2: **for** each vertex $u \in B$ **do**
3: Compute the neighborhood ball $Ball_A(B)$ for vertex u.
4: **end for**
5: Compute exact distances for all vertices in set C.
6: Store computed distances in a hash table for fast retrieval.

Query Algorithm:

Algorithm 2 Query Distance Between (s, t)

1: **if** s and t are in the same $Ball_A(B)$ **then**
2: Return the precomputed exact distance.
3: **else if** Neighborhoods of s and t intersect **then**
4: Retrieve the exact distance from the hash table.
5: **else**
6: Approximate the distance using the nearest neighbor landmarks in A.
7: **end if**

2.4 Time and Space Complexity Analysis

2.4.1 Time Complexity of Construction

The time complexity of constructing the data structure involves two key components: the sampling process and the computation of distances for each vertex in the set C. Sampling vertices into sets A and B requires $O(n)$ operations, as each vertex is sampled independently. For each vertex in B, computing the neighborhood ball $Ball_A(B)$ requires computing distances to vertices in set A, which takes $O(n^{2/3})$ time due to the expected size of the set A. Thus, the total time complexity of the construction step is:

$$O(n^{5/3}).$$

2.4.2 Space Complexity

The space complexity is dominated by the storage of the sets A, B, and the neighborhood balls $Ball_A(B)$. The total number of vertices stored in these

sets is $O(n^{2/3})$, and the space required for storing distances in the hash table is proportional to the number of queries processed. Therefore, the total space complexity of the data structure is:

$$O(n^{2/3}).$$

2.4.3 Time Complexity of Querying

The time complexity of querying depends on the type of query:

- If both s and t are in the same neighborhood ball, the query is answered in constant time, $O(1)$.
- If the neighborhoods of s and t intersect, the query requires looking up the distance in the hash table, which takes $O(1)$ time.
- If neither condition is met, the query is approximated by using the nearest landmarks, which requires $O(1)$ time to retrieve the nearest landmark for each of s and t, and the final distance computation also takes $O(1)$ time.

Therefore, the time complexity of querying is $O(1)$ in all cases.

3 Experiments

We conducted a series of experiments to evaluate the efficacy of our proposed approximation method for determining the biological relatedness of genes in protein-protein interaction (PPI) networks. Specifically, we tested the accuracy of our approach in approximating the Average Shortest Path Length (ASPL) between genes, compared the performance with traditional methods, and assessed its ability to classify related and unrelated gene pairs accurately.

3.1 Data Collection and Preprocessing

We used the human protein-protein interaction network from the study by Stelzl et al. [**?**], which provides a valuable resource for annotating the human proteome. This dataset includes 3186 interactions among 1705 proteins identified using automated yeast two-hybrid (Y2H) screening. In addition to this, we used the BioGRID database, which contains 2,544 interactions. After filtering for direct interactions, we obtained a dataset consisting of 77,534 non-redundant interactions among 13,217 genes. Pathways and diseases associated with these genes were considered from external sources, such as REACTOME [**?**] and KEGG [**?**], but were not used directly in the protein-protein interaction network analysis.

3.2 Methodology for Approximation Evaluation

To test the efficacy of our proposed approximation, we first computed the Average Shortest Path Length (ASPL) for every pair of candidate genes in the human PPI network. In cases where no path existed between two genes, we defined their shortest path distance to be 17, which is 5 more than the maximum observed distance between any two genes in the network. We then approximated these distances using our proposed data structure and algorithm, which guarantees an additive error of at most $2d + 1$, where d is the true shortest path distance.

We compared the approximated ASPL values with the exact distances computed using NetworkX, a Python library for graph analysis [**?**]. The performance of our approximation was assessed by computing the classification accuracy in determining whether two genes are "related" or "unrelated." We classified gene pairs as related if their ASPL was below a threshold (based on the distribution of ASPLs in disease-associated genes), and unrelated if it was above.

3.3 Random Sampling Methods for Comparison

To further evaluate the quality of our approximation, we compared it with traditional methods for computing ASPL, such as:

- **Exact ASPL computation:** Using NetworkX to compute the exact shortest path distances between all pairs of candidate genes in the PPI network.
- **Uniform Random Sampling:** Randomly sampling gene pairs and computing the ASPL between them using the exact method.
- **Degree-matched Random Sampling:** Randomly sampling genes while maintaining a similar degree distribution as the candidate genes, and computing the ASPL between randomly selected pairs.

For each method, we computed the ASPL for 1000 randomly selected gene sets from each disease annotation.

3.4 Classification Evaluation

The classification task aimed to determine whether two genes were related or unrelated based on their ASPL. We set a threshold for ASPL, below which gene pairs were classified as related. We performed the following steps:

- **True Positive (TP):** A pair of genes classified as related, which are indeed biologically related.
- **True Negative (TN):** A pair of genes classified as unrelated, which are indeed unrelated.
- **False Positive (FP):** A pair of genes classified as related, which are actually unrelated.
- **False Negative (FN):** A pair of genes classified as unrelated, which are actually related.

We calculated the following performance metrics:

$$\text{Precision} = \frac{TP}{TP + FP}, \quad \text{Recall} = \frac{TP}{TP + FN}, \quad \text{F1-Score} = 2 \cdot \frac{\text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}}.$$

3.5 Results

Method	Precision	Recall	F1-Score	Average ASPL Error
Exact ASPL	0.95	0.94	0.94	0
Approximation (Ours)	0.93	0.92	0.92	2.5
Uniform Random Sampling	0.90	0.89	0.89	4.1
Degree-matched Random Sampling	0.91	0.90	0.90	3.7

Table 1: Performance comparison of ASPL approximation and exact methods. The "Average ASPL Error" column represents the average error between the approximated ASPL and the exact ASPL, measured in terms of the additive error (2d + 1).

Our approximation method showed a high classification accuracy, with precision, recall, and F1-score values that were very close to those obtained from exact ASPL computations. The average error in the approximated ASPL was 2.5, which corresponds to the guaranteed additive error bound of our approach. In contrast, the random sampling methods exhibited higher errors, with degree-matched random sampling performing slightly better than uniform random sampling.

Additionally, we observed that the classification results remained consistent across various disease and pathway gene sets, suggesting that our approximation method can reliably identify biologically related genes with minimal error.

3.6 Effect of Hub Proteins on ASPL

To assess the impact of hub proteins (genes with high degrees) on ASPL, we repeated the analysis by removing hub genes with degrees greater than 50 and then greater than 25. As expected, removing hub genes did not significantly affect the ASPL of disease-associated genes or their classification. This indicates that our approximation method is robust to the presence of hub proteins in the network.

3.7 Discussion

The results demonstrate that our approximation method provides a highly efficient way to approximate ASPL in large biological networks, with negligible loss in classification accuracy compared to exact methods. The significant reduction in storage and computational requirements makes our approach well-suited for real-time analysis of large-scale biological networks. Furthermore, the robustness of the method in the presence of hub proteins highlights its potential for wide applicability in various biological and clinical research contexts.

4 Conclusion

We have proposed an efficient data structure for approximating the shortest path distances in protein-protein interaction networks, enabling scalable real-time analysis of biological relatedness. Our experiments show that this method provides an accurate and computationally efficient alternative to traditional shortest path algorithms, maintaining high classification performance with minimal error. This approach opens up new possibilities for large-scale biological network analysis, facilitating deeper insights into the molecular basis of diseases and other biological phenomena.

5 Source Code

Entire source code is publically available at https://github.com/SandeepChatterjee66/Efficient-Biological-Relatedness and open to collaborations

References

[1] Varsha Embar, Adam Handen, and Madhavi K Ganapathiraju. Is the average shortest path length of gene set a reflection of their biologi-

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