Paper Title

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Here should come the abstract.

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1. Introduction

Studying interactions between proteins has been of utmost importance in understanding how proteins work collectively to govern cellular function.[1,2] Such collection of interactions among proteins is called a protein interaction network. Mathematically, a protein interaction network is often modeled as an edge-weighted undirected graph where each node denotes a protein and each edge represents an interaction between a pair of proteins. The weight of an edge denotes the level of confidence that this interaction truly exists.

One of the key outcomes of computational analysis of protein interaction networks is identification of signaling pathways. A signaling pathway is a series of proteins in which each protein participates in transmitting biological information by modifying its successor through an interaction. Thus, signaling pathways can be viewed as simple paths in protein interaction networks.[3]

The confidence value of an interaction between two proteins is often considered as the probability that a signal is transmitted between those two proteins. Thus, the probability that a signal moves through a pathway is the product of the confidence values of its constituting interactions. Under this model, Scott et al. conjectured that a signal tends to move through the most probable pathway.[4] They showed that such pathways yield signaling pathways, and thus help in reconstructing signaling networks. Following defines the problem of identifying the most probable pathway in a protein interaction network.

Problem Consider a protein interaction network (V, E, λ) where V denotes the set of proteins, $E = \{(u, v)|u, v \in V\}$ denotes the set of interactions, and the function $\lambda() : E \Rightarrow [0, 1]$ denotes interaction confidence for each interaction in E. Assume that we are given a set of starting proteins $S \subseteq V$ and a set of target proteins $T \subseteq V$. Given a path length denoted by a positive integer m, the problem is to find a simple path $\Phi = v_1 \rightarrow v_2 \rightarrow \ldots \rightarrow v_m$, where $\prod_{i=1}^{m-1} \lambda(v_i, v_{i+1})$ is maximum among all paths with $v_1 \in S$, $v_m \in T$ and $v_i \in V \forall i \in \{1, 2, \ldots, m\}$.

The problem above is equivalent to finding a simple path $\phi = v_1 \to v_2 \to \ldots \to v_m$, where $\sum_{i=1}^{m-1} -\log\ \lambda(v_i, v_{i+1})$ is minimum among all paths with $v_1 \in S$, $v_m \in T$ and $v_i \in V \forall i \in \{1, 2, \ldots, m\}$. The traveling-salesman problem is polynomial-time reducible to this problem;[4] therefore it is NP-hard. They developed a method using a technique devised by Alon et al.,[5] called *color-coding.* The basic idea of this method is to randomly assign each node in the graph one of m different colors, and search for an optimal pathway in the restricted domain of colorful pathways. A pathway is colorful if and only if all of its nodes are in different color. Finding a colorful path is computationally much cheaper than finding a path without assigning colors. The drawback is that the optimal path may not be colorful in a random color assignment. If that happens, the color coding method fails to find the true optimal result. To deal with this, color coding method repeats the coloring process for several iterations. The confidence in the optimality of the result monotonically increases with each iteration until it reaches a given level of confidence that the unknown optimal pathway was among the colorful ones in at least one of these iterations. As we elaborate later in section 2, the confidence value depends solely on the pathway length m and does not capitalize on readily available information such as the network topology and color assignment. As a result, the method provides a theoretically correct but very conservative confidence value. Hence it requires many iterations in order to achieve a given confidence level, leading to an unnecessarily innefficient running time performance.

Gülsoy et al.[6] presented an enhanced color-coding technique called *k-hop coloring.* A colored network is k-hop colorable if the shortest path between all pairs of same-color nodes is more than k hops in length. This method exploits the network topology and the node colors to assign the network a maximal value k such that the network is k-hop colorable. This additional piece of information allows for higher success probability at each iteration, yielding fewer iterations than that by Scott et al. However, subnetworks with high connectivity quickly diminish the ability to k-hop color the whole network for large values of k. For example, a network containing a clique of size m cannot be colored with $(m-1)$-hop coloring using m colors.[6]

Contribution In this paper, we consider the problem of finding signaling pathways in protein interaction networks. We develop a new coloring method that overcomes the bottlenecks of exisiting coloring methods by Scott et al.[4] and Gülsoy et al.[6] Our contribution comes from a deeper understanding of the relation between network topology, random color assignment and confidence value. We assign a k value to each node individually by studying the colors of all the nodes in the network. The k value of a node v at an iteration indicates that there is no other node u that is reachable from v in k hops such that both u and v have the same color. For each node, the k value is the largest integer that satisfies the above constraint. Thus, different nodes in the network may have different k values. We also study how this reflects on the resulting success probability for each iteration. Given different k values for each node on a pathway, we show how to obtain a bound on success probability.

Based on these findings, We present a new method for detecting signaling pathways in protein interaction networks using an enhanced k-hop coloring technique. Given the parameter pathway length m, we start by randomly assigning one of m colors to each node in the graph, we then extract the optimal colorful pathway. We then calculate our new bound on success probability. We repeat this process until the cumulative success probability is at least equal to a given confidence level. Although our theoretical findings are based on assuming the knowledge of the k values assigned to the unknown global optimal pathway, we empirically demonstrate that the local optimal pathway extracted from the domain of colorful pathways yields correct confidence values.

The coloring methods developed by Gülsoy et al.[6] and Scott et al.[4] yield special cases of our method. The first method is our method in the special case of all the nodes in the network having the same k value. The second method is our method in the special case of all the nodes in the network having k value $= 0$. Hence, our method is guaranteed to perform at least as good as both of them in these special cases, and better in the general case.

We provide validation experiments to test the biological significance of our results. We use *weight p-value* and *functional enrichment* as validation measures. We also compare the performance of our method against the one presented by Scott et al.[4] with respect to how fast our method reaches a given confidence level as opposed to theirs.

The rest of the paper is organized as follows. Section 2 discusses the background and related work. Section 3 explains how to obtain a tighter bound on success probability and describes our enhanced k-hop coloring method. Section 4 shows the experiments performed and their results. Section 5 is the conclusion of the paper.

2. Background

A number of methods have been developed so far to identify signaling networks from protein interaction networks. These methods differ in the way they formulate the problem. Among them, Zhao et al.[7] formulated a linear optimization problem that finds the maximum weighted subnetwork with a given size. The main difference of this approach from this paper is that it is concerned with finding signaling subnetworks rather than linear pathways. Kelley et al.[3] detected conserved signaling pathways between related organisms by performing global alignment between their protein interaction networks. They scored each pathway in terms of the probability of true homology between aligned pair of proteins, as well as the probability of true interactions between pairs of proteins along the pathway. Shlomi et al.[8] introduced QPath, a method for querying protein interaction networks for pathways using known homologous pathways as queries. They scored results based on their similarity to the query, number of insertions and deletions used, as well as the reliability of their interactions. Both Kelley et al.[3] and Shlomi et al.[8] are comparative methods. They require knowledge of multiple interaction networks. Thus, they solve a related, yet different, computational problem than the one considered in this paper.

Lu et al.[9] presented a divide-and-conquer algorithm to find signaling subnetworks in protein interaction networks. They recursively partitioned the network into two sets of vertices, enumerated substructures present in each set, and then built larger subnetworks from them. They assumed that all edges have the same weight. They scored the resulting subnetworks based on the similarity of expression profiles of their nodes to the given source and destination nodes. This method formulates a different objective. It aims to detect paths whose proteins are highest in expression similarity, and thus it does not utilize the confidence in the interactions.

Steffen et al.[10] studied detecting signaling pathways in protein interaction networks as guided by expression data. They listed all pathway candidates in a protein interaction network using exhaustive search. They scored each candidate based on how similar the expression profiles of its genes are. Bebek et al.[11] presented a method called PathFinder for finding new signaling pathways using association rules of known ones. They started with mining association rules for known pathways, guided by the knowledge of functional annotations of their proteins. They then performed an exhaustive search for candidate pathways. From these candidates, they selected the ones having at least a certain number of the known association rules and an average interaction weight above a given threshold. The drawback of both of these methods is that the time complexity of exhaustive graph search is exponential in terms of the network size, and hence is very inefficient.

Gitter et al.[12] presented a method for discovering signaling pathways by adding edge orientation to protein interaction networks. They selected an optimal orientation of all edges in the network that maximizes the weights of all satisfied length-bound paths. They say a path is satisfied if it follows the same direction along its edges from a source node to a destination node. They proved that this problem is NP-hard. They provided two approximation algorithms for it based on available solution methods for weighted Boolean satisfiability, and a third algorithm based on probabilistic selection. As shown in their results, these methods do not scale well with increasing the number of source and destination nodes and the required path length.

The closest studies to that presented in this paper are those by Scott et al.[4] and Gülsoy et al.[6] The former detected signaling pathways in protein interaction networks using color coding. The latter developed topology-aware color coding for network alignment. We describe both methods in detail in section 1. Both methods run multiple coloring iterations. Let us denote the probability that the coloring at an iteration is successful (i.e. true optimal path is colorful) with P_s. The probability that at least one out of r iterations is successful is $1-(1-P_s)^r$. Following from this, in order to insure confidence of at least ϵ $(0 \leq \epsilon \leq 1)$, they run r iterations, such that $1-(1-P_s)^r \geq \epsilon$. Both methods calculate success probability as

$$P_s = \frac{m!}{N_c} \tag{1}$$

where N_c is the number of coloring assignments possible for the optimal pathway. They differ in the way they compute N_c. Scott et al.[4] calculated $N_c = m^m$. Gülsoy et al.[6] calculated a bound $N_c \leq (m-k)^{m-k} \prod_{i=0}^{k-1}(m-i)$ where k is the value assigned to the network such that it is k-hop colorable. Notice that in equation 1, smaller values for N_c are desirable. This is because small values for N_c increase success probability, and thus reduces the number of iterations needed to attain a given confidence level ϵ. This paper develops a novel method that computes a much smaller upper bound on N_c than both Scott et al. and Gülsoy et al., hence a better lower bound on P_s.

3. Methods

In this section, we start by properly formulating the problem and defining common terms that we use in our methods. We then present new thoughts about pathway detection using color coding. We study the opportunity of more involving of network topology in our calculation to obtain a better success probability, and hence needing less number of iterations and improving performance. Last, we present an enhanced color-coding method for detecting pathways in protein interaction networks.

3.1. *Success Probability: a Tighter Bound*

Our key contribution is to establish the relationship among network topology, node colors and sucess probability in a single iteration of color coding. In this section, we focus on one coloring iteration and describe how we compute the probability of success in that iteration.

Assume that we are given a protein interaction network similar to the one described in section 1, denoted by $G = (V, E, w)$, where $w(u, v) = -\log \lambda(u, v)$. Also assume that the colors of the nodes are already assigned in the current iteration. We denote the set of possible colors with $\{c_1, c_2, \ldots, c_m\}$ and denote the color of node $v \in V$ with $c(v)$.

Consider any colorful path with m nodes. The number of ways to assign colors to the nodes of that path while keeping it colorful is $m!$. Notice that this is equal to the numerator in equation 1 for probability of success. The denominator in that equation, denoted by N_c, is the total number of ways to color that path regardless of whether it yields colorful or not. Before we discuss how we compute N_c, we describe the following concepts.

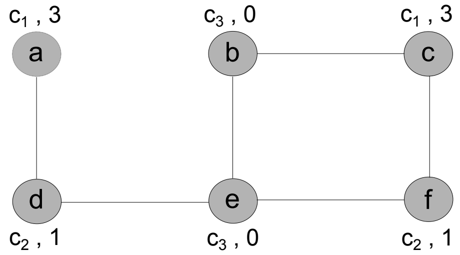


Fig. 1. A hypothetical protein interaction network with six nodes {a, b, c, d, e, f}. The network is colored using three colors $\{c_1, c_2, c_3\}$. Each node carries two labels. The label on the left denotes the color assigned to this node. The one on the right is the node's k_{max} value. For instance node d is assigned to color c_2 and its k_{max} value is 1 (i.e., there is no other node assigned to color c_2 within 1-hop of node d).

(1) k neighborhood of a node. Let $v \in V$ be a node in G, and k be a natural number. $\Psi_k(v)$ is the set of nodes where $\forall u \in V \backslash \{v\}$, $u \in \Psi_k(v)$ if and only if u is reachable from v in k hops of less. We call $\Psi_k(v)$ the k neighborhood of v. Figure 1 shows an example of a colored network. In this example, $\Psi_1(a) = \{d\}$ because the node d is the only node that is reachable from the node a in 1 hop (or less). Similarly, $\Psi_1(f) = \{c, e\}$, $\Psi_2(a) = \{d, e\}$ and $\Psi_2(f) = \{c, e, b, d\}$.

(2) k_{max} value of a node. Let $v \in V$ be a node in G. $k_{max}(v)$ is the maximal value of k such that $\forall u \in \Psi_k(v)$: $c(u) \neq c(v)$. Figure 1 also shows the k_{max} values for the nodes in the network. For example, $\forall u \in \Psi_1(f) = \{c, e\}$, $c(u) \neq c(f)$. If we try to expand to $\Psi_2(f) = \{c, e, b, d\}$, we find that $c(d) = c(f) = c_2$. Therefore $k_{max}(f) = 1$. Similarly, $k_{max}(a) = 3$ and $k_{max}(b) = 0$.

(3) k_{max} configuration of a path. Let $\Phi = v_1 \rightarrow v_2 \rightarrow \ldots \rightarrow v_m$ be a path of length m in G. The k_{max} configuration of Φ is the sequence $[k_{max}(v_1), k_{max}(v_2), \ldots, k_{max}(v_m)]$.

Our approach relies on individual max_k values of all nodes in an optimal path. Assuming

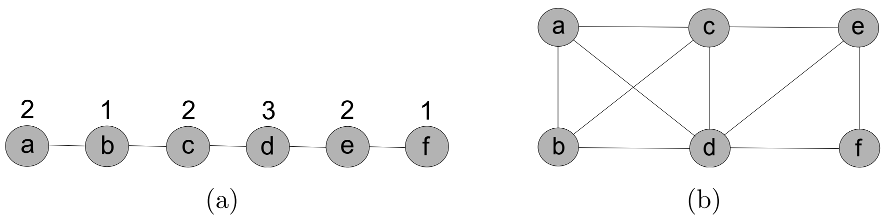


Fig. 2. (a) An example 6-node path with its *max_k* configuration shown above it. Each *max_k* value translates to the number of nodes that have to be of different color on either direction. (b) The corresponding constraint graph W: each pair of adjacent nodes have to be of different color. Finding the value of the chromatic polynomial $P(W, m)$ yields the number of coloring possibilities for the path under the given constraints.

knowledge of the *max_k* configuration of the optimal path, we use it to calculate N_c under the restrictions induced by these values. We also assume that each node in the path is not connected to any other nodes except the ones before and after it in the path. This assumption is valid because any more connections will only induce more coloring restrictions, causing N_c to decrease; therefore we get a solid upper bound on N_c, hence a solid lower bound on P_s according to equation (1). For a given node v in a given path, all $max\_k(v)$ nodes in either direction from v are not allowed to have the same color as v. We represent this rule as an unweighted constraint graph $W = (H, L)$ where H is its set of nodes and L is its set of edges. H contains a node corresponding to each node in the path, and L contains an edge for each pair of nodes that are not allowed to have the same color, according to the aforementioned rule. Figure 2 shows an example of a path, its *max_k* configuration and the corresponding constraint graph W. The problem now translates to calculating the value of the chromatic polynomial $P(W, m)$: the number of ways of coloring W using m colors without any pair of adjacent nodes having the same color. We calculate this value using the following edge-contraction recursive rule based on the fundamental reduction theorem:[13]

$$P(W, m) = P(W - uv, m) - P(W/uv, m) \tag{2}$$

where u and v are any pair of adjacent nodes, $W - uv$ is the graph W after removing the edge uv, and W/uv is the graph W after merging the nodes u and v.

According to this method, the value of N_c for the example path shown in Figure 2(a) is 5,760, while Scott et al.[4] and Gülsoy et al.[6] would respectively yield N_c = 46,656 and 18,750 for the same example. Such a decrease in the value of N_c leads to an increase in the value of P_s according to equation (1).

3.2. *Method: Enhanced k-hop Coloring*

The approach introduced in the previous section for calculating success probability assumes the knowledge of the *max_k* configuration of the optimal path. Needless to say, this is not the case. We present a conjecture that we can instead use the *max_k* configuration of the local colorful optimal path. We empirically show that this substitution serves the purpose. Our method reports the optimal colorful path in each iteration and computes P_s based on its *max_k* configuration. We also keep a heap of the top 100 reported paths to cover the possibility of a pathway having a suboptimal score. The method is detailed as follows:

(1) Initializations:

(i) $M \Leftarrow \{1, 2, ..., m\}$: the set of all m colors.
(ii) $P \Leftarrow 0$: overall success probability.
(iii) $H \Leftarrow \{\}$: heap of top 100 paths.

(2) $\forall v \in V$, $c(v) \Leftarrow$ a color uniformly drawn from M.
(3) $\forall v \in V$, the minimum weight of a colorful path colored only using $M' \subseteq M$, starting within S and ending at v, can be dynamically tabulated using the following recurrence:[4]

$$W(v, M') = \min_{u:c(u)\in(M'\backslash\{c(v)\})} W(u, M'\backslash\{c(v)\}) + w(u, v), |M'| > 1 \tag{3}$$

where $W(v, \{c(v)\}) = 0$ if $v \in S$ and ∞ otherwise.
(4) Report path X whose weight $= \min_{v \in V} W(v, M)$.
(5) Add X to H.
(6) Compute N_c using the max_k configuration of X according to the chromatic polynomial recurrence detailed in equation (2).
(7) Compute $P_s \Leftarrow m!/N_c$.
(8) Update $P \Leftarrow 1 - (1 - P)(1 - P_s)$.
(9) Repeat from step (2) until $P \geq \epsilon$.

4. Experiments

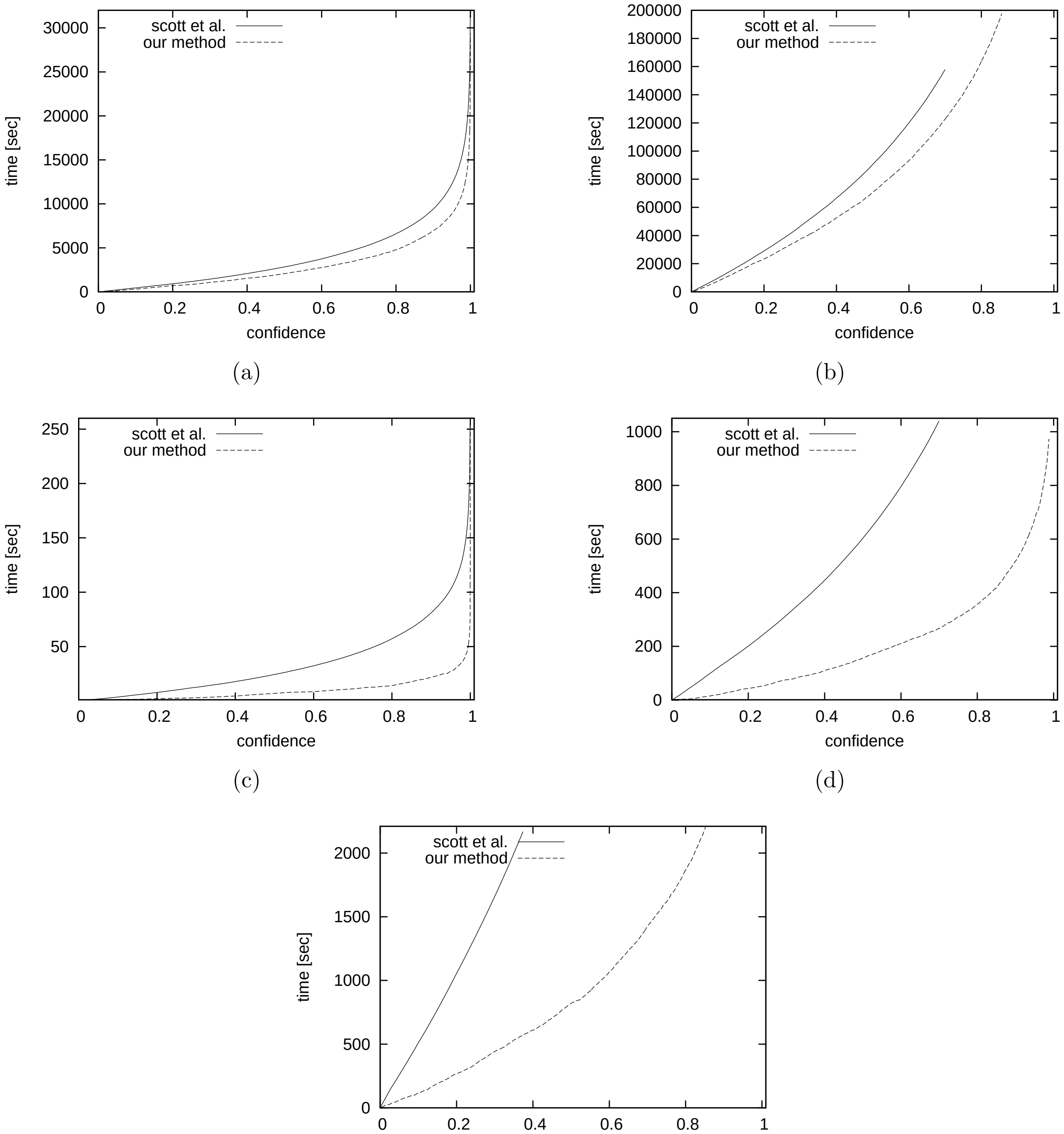
In this section, we evaluate our method on real datasets. We implemented our method in Java language. We ran our experiments on system details

Datasets In our experiments, we used two datasets of protein interactions in Homo Sapiens and Rattus Norvegicus from MINT[14] (the Molecular INTeraction database). The first one is a large dataset of 15472 interactions among 6122 proteins. The second one is a smaller dataset of 806 interactions among 631 proteins. Each interaction is described by two interacting proteins and a reliability score between 0 and 1 that represents the level of confidence that this interaction truly exists. MINT calculates reliability scores of interactions using a heuristic formula of available evidence, including the size and type of the experiment reporting the interaction, sequence similarity of ortholog proteins and the number of publications supporting the interaction.[15]

We use the negative logarithm of MINT reliability scores as edge weights. In all experiments, we find pathways starting within the set of membrane proteins and ending within the set of transcription factors. We use the Gene Ontology database[16] to identify membrane proteins and transcription factors of each dataset. We identify membrane proteins as the ones under the terms GO:0005886 and GO:0004872, and transcription factors as the proteins under the terms GO:0000988, GO:0001071 and GO:0006351.

4.1. *Performance assessment and comparison*

We run an experiment to measure how fast the value of confidence rises with each iteration in both our method and the one presented by Scott et al.[4] We run each method for 500



(a)

(b)

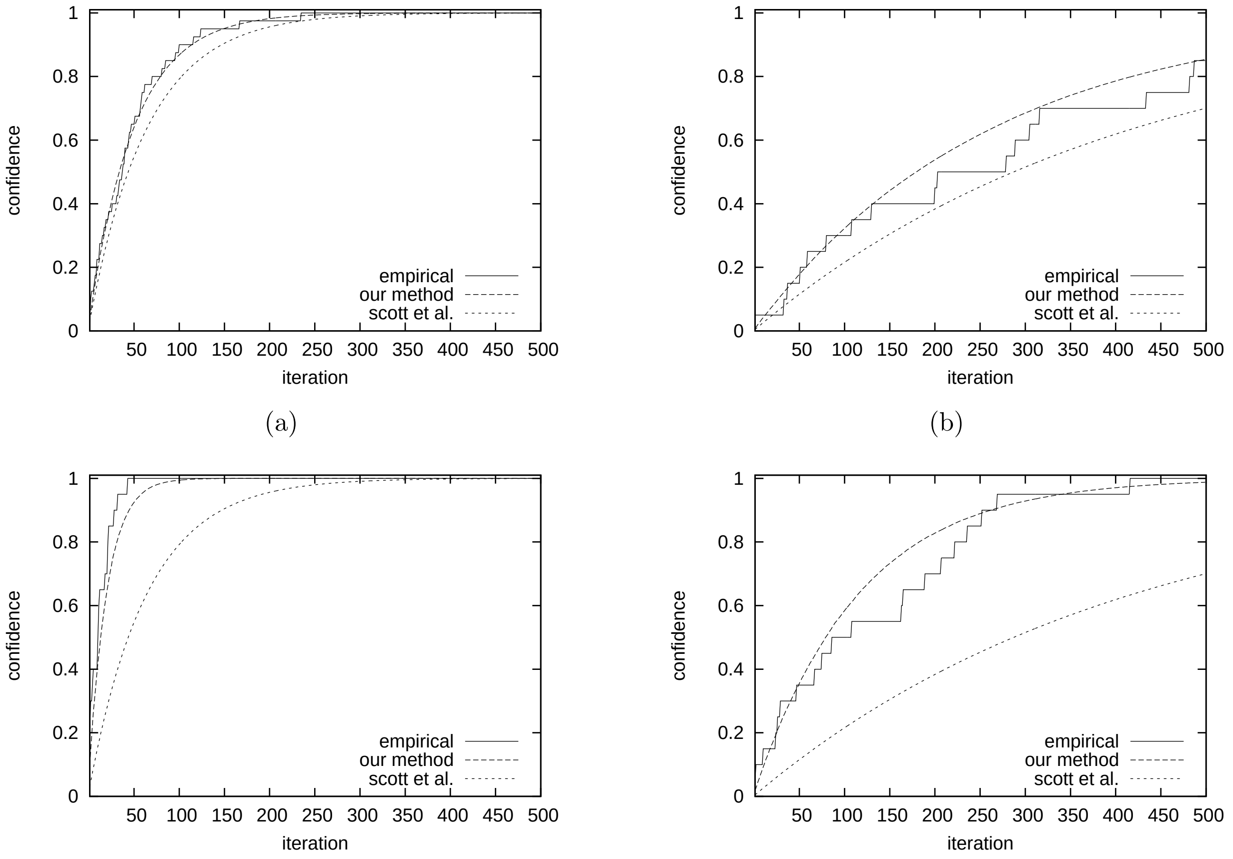
(c)

(d)

(e)

Fig. 3. blah blah

iterations and measure the overall confidence after each iteration is finished. We also compare these results with the practical confidence, which is the probability of finding the optimal pathway as practically observed. To compute the practical confidence, we run 500 coloring iterations and assign each iteration a value $s \in \{0, 1\}$, where $s = 1$ if the optimal pathway is found in this iteration or in a preceding one, and $s = 0$ otherwise. We repeat this experiment



(a)

(b)

(c)

(d)

Fig. 4. write your caption here (a) asdakj (b) anslkjal

multiple times and take the average values of s for each iteration as the practical confidence of this iteration. Figure 4 shows the confidence value as more iterations finish, for our method and Scott et al. and also the practical confidence value. The figure shows a gap between Scott et al. confidence and practical confidence, which is expected because of the conservative way they use to calculate success probability of an iteration, as discussed in section 2. This gap increases as the path length parameter increases. Our method closes this gap and produces confidence values that are closer to the practical confidence values. The figure also shows that our method produces higher confidence values than Scott et al. for the same number of iterations.

We also measure the total time taken by our method to reach a given confidence level as opposed to that of Scott *et al.*[4] We run both methods for 500 iterations and measure, after each iteration, the confidence level reached and the overall time taken by both methods. Figure 3 shows that our method takes less time than Scott et al. to achieve the same level of confidence. The figure also shows that the our performance lead increases as the path length parameter increases.

Table 1. Table caption should come here.

Dataset	Path Length								
	6			7			8		
	μ	θ	Z	μ	θ	Z	μ	θ	Z
H.sapiens	5.906	0.129	5.409	7.074	0.130	5.477	8.341	0.221	5.764
R.norvegicus	4.975	4.540	0.889	7.307	5.025	1.453	8.457	4.858	1.467

4.2. *Validation Experiments*

So far we have shown that our method outperforms existing coloring strategies in terms of the running time performance. In this section, we evaluate the biological significance of the results we can find using our method.

It is worth mentioning that our method returns the same results as Scott *et al.*[4] when both of them are allowed to reach a high confidence value (such as 99% confidence). The main difference is that our method scales to larger networks and longer paths. Therefore, here we will only focus on the results obtained by our method.

4.2.1. *Statistical significance of the results*

In this section

For each dataset we use, we should obtain the 99 percent confidence optimal pathway and compare it with optimal pathways obtained we obtain from random networks. We generate random networks by shuffling edges of the original network. The weight p-value is the percentage of cases where the algorithm produces a more optimal pathway when run on one of these random networks.

4.2.2. *Validation using Functional Enrichment*

For each dataset, we we obtain the 99 percent confidence optimal pathway and test its functional enrichment. For each GO term appearing on the dataset proteins, we count the total number of proteins annotated by it and the number of proteins in the resulting pathway annotated by it. We use these numbers, along with the total number of proteins and the number of proteins in the pathway, as parameters for a hypergeometric test (I still have to develop further understanding about the details of this test). The maximum enrichment value for any of the tested GO terms gives us the final functional enrichment p-value.

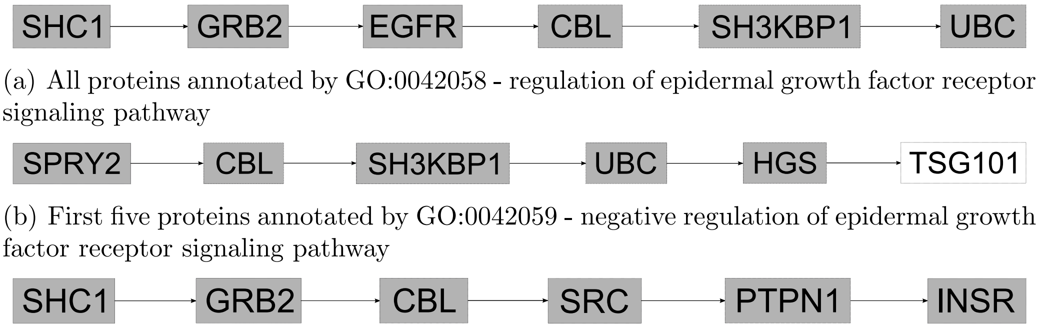
4.3. *Discussing paths found*

5. Conclusion

Here goes the conclusion.

References

1. B. Schwikowski, P. Uetz and S. Fields, *Nature Biotechnology* **18**, 1257 (December 2000).
2. P. Uetz, L. Giot, G. Cagney, T. A. Mansfield, R. S. Judson, J. R. Knight, D. Lockshon, V. Narayan, M. Srinivasan, P. Pochart, A. Qureshi-Emili, Y. Li, B. Godwin, D. Conover,



(a) All proteins annotated by GO:0042058 - regulation of epidermal growth factor receptor signaling pathway

(b) First five proteins annotated by GO:0042059 - negative regulation of epidermal growth factor receptor signaling pathway

(c) All proteins annotated by GO:0046875 - ephrin receptor binding

Fig. 5. Caption goes here

T. Kalbfleisch, G. Vijayadamodar, M. Yang, M. Johnston, S. Fields and J. M. Rothberg, *Nature* **403**, 623 (February 2000).

3. B. P. Kelley, R. Sharan, R. M. Karp, T. Sittler, D. E. Root, B. R. Stockwell and T. Ideker, *Proceedings of the National Academy of Sciences* **100**, 11394 (September 2003).
4. J. Scott, T. Ideker, R. M. Karp and R. Sharan, Efficient algorithms for detecting signaling pathways in protein interaction networks, in *Proceedings of the 9th Annual international conference on Research in Computational Molecular Biology*, RECOMB'05 (Springer-Verlag, Berlin, Heidelberg, 2005).
5. N. Alon, R. Yuster and U. Zwick, *J. ACM* , 844 (1995).
6. G. Gülsoy, B. Gandhi and T. Kahveci, Topology aware coloring of gene regulatory networks, in *Proceedings of the 2nd ACM Conference on Bioinformatics, Computational Biology and Biomedicine*, BCB '11 (ACM, New York, NY, USA, 2011).
7. X.-M. Zhao, R.-S. Wang, L. Chen and K. Aihara, *Nucleic Acids Research* **36**, p. e48 (2008).
8. T. Shlomi, D. Segal, E. Ruppin and R. Sharan, *BMC Bioinformatics* **7**, p. 199 (2006).
9. S. Lu, F. Zhang, J. Chen and S.-H. Sze, *Algorithmica* **48**, 363 (August 2007).
10. M. Steffen, A. Petti, J. Aach, P. D'haeseleer and G. Church, *BMC Bioinformatics* **3**, p. 34 (2002).
11. G. Bebek and J. Yang, *BMC Bioinformatics* **8**, p. 335 (2007).
12. A. Gitter, J. Klein-Seetharaman, A. Gupta and Z. Bar-Joseph, *Nucleic Acids Research* **39**, p. e22 (2011).
13. F. Dong, K. Koh and K. Teo, *Chromatic Polynomials And Chromaticity of Graphs* (World Scientific Pub., 2005).
14. A. Chatr-aryamontri, A. Ceol, L. Montecchi-Palazzi, G. Nardelli, M. V. Schneider, L. Castagnoli and G. Cesareni, *Nucleic Acids Research* **35**, 572 (2007).
15. A. Ceol, A. Chatr Aryamontri, L. Licata, D. Peluso, L. Briganti, L. Perfetto, L. Castagnoli and G. Cesareni, *Nucleic Acids Research* **38**, D532 (2010).
16. M. Ashburner, C. A. Ball, J. A. Blake, D. Botstein, H. Butler, J. M. Cherry, A. P. Davis, K. Dolinski, S. S. Dwight, J. T. Eppig, M. A. Harris, D. P. Hill, L. Issel-Tarver, A. Kasarskis, S. Lewis, J. C. Matese, J. E. Richardson, M. Ringwald, G. M. Rubin and G. Sherlock, *Nature genetics* **25**, 25 (May 2000).