# BRIDES: A New Fast Algorithm and Software for Characterizing Evolving Similarity Networks Using Breakthroughs, Roadblocks, Impasses, Detours, Equals and Shortcuts 

Etienne Lord, Margaux Le Cam, Éric Bapteste, Raphaël Méheust, Vladimir
Makarenkov, François-Joseph Lapointe

## To cite this version:

Etienne Lord, Margaux Le Cam, Éric Bapteste, Raphaël Méheust, Vladimir Makarenkov, et al.. BRIDES: A New Fast Algorithm and Software for Characterizing Evolving Similarity Networks Using Breakthroughs, Roadblocks, Impasses, Detours, Equals and Shortcuts. PLoS ONE, 2016, 11 (8), pp.e0161474. 10.1371/journal.pone.0161474 . hal-01361753

HAL Id: hal-01361753
https://hal.sorbonne-universite.fr/hal-01361753
Submitted on 7 Sep 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. publics ou privés.

Distributed under a Creative Commons Attribution 4.0 International License

Citation: Lord E, Le Cam M, Bapteste É, Méheust R, Makarenkov V, Lapointe F-J (2016) BRIDES: A New Fast Algorithm and Software for Characterizing Evolving Similarity Networks Using Breakthroughs, Roadblocks, Impasses, Detours, Equals and Shortcuts. PLoS ONE 11(8): e0161474. doi:10.1371/ journal.pone. 0161474

Editor: Xia Li, College of Bioinformatics Science and Technology, CHINA

Received: April 27, 2016

Accepted: August 6, 2016
Published: August 31, 2016
Copyright: © 2016 Lord et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The R and C++ source codes are available from the Github repository (https://github.com/etiennelord/BRIDES/) with a GPL version 3 license. The sample networks (Figs 1 and 2) are located in either the R or $\mathrm{C}++$ source directories. The source code for the simulations (Fig 3 ) is located in the Simulation directory of the github repository. The genome similarity networks (Fig 4, Table 2) are available in the GenomeNetwork directory.

# BRIDES: A New Fast Algorithm and Software for Characterizing Evolving Similarity Networks Using Breakthroughs, Roadblocks, Impasses, Detours, Equals and Shortcuts 

Etienne Lord ${ }^{1,2}$, Margaux Le Cam ${ }^{2}$, Éric Bapteste ${ }^{3,4}$, Raphaël Méheust ${ }^{3}$, Vladimir Makarenkov ${ }^{1}$, François-Joseph Lapointe ${ }^{2 *}$<br>1 Département d'informatique, Université du Québec à Montréal, Montréal, Québec, Canada,<br>2 Département de sciences biologiques, Université de Montréal, Montréal, Québec, Canada, 3 Sorbonne Universités, UPMC Université Paris 06, Institut de Biologie Paris-Seine, Paris, France, 4 CNRS, UMR7138, Institut de Biologie Paris-Seine, Paris, France<br>* francois-joseph.lapointe @umontreal.ca


#### Abstract

Various types of genome and gene similarity networks along with their characteristics have been increasingly used for retracing different kinds of evolutionary and ecological relationships. Here, we present a new polynomial time algorithm and the corresponding software (BRIDES) to provide characterization of different types of paths existing in evolving (or augmented) similarity networks under the constraint that such paths contain at least one node that was not present in the original network. These different paths are denoted as Breakthroughs, Roadblocks, Impasses, Detours, Equal paths, and Shortcuts. The analysis of their distribution can allow discriminating among different evolutionary hypotheses concerning genomes or genes at hand. Our approach is based on an original application of the popular shortest path Dijkstra's and Yen's algorithms. The C++ and R versions of the BRIDES program are freely available at: https://github.com/etiennelord/BRIDES.


## Introduction

Network structures provide useful representations of interactions between the elements of complex systems [1,2]. They can, for example, represent relationships between microbial communities in different environments [3] or between proteins in different bacteria and eukaryotes [4]. The abundance of the network elements (i.e. represented by nodes) as well as their interactions (i.e. represented by edges) often vary over time. Comparing evolving networks containing sets of attributes (or annotations) at their nodes is currently becoming central to different fields of biology, including ecology, evolution, cell biology and medicine [1, 5-7]. For example, genome similarity networks, where each node represents a genome and the edge weights correspond to the number of shared gene families between genomes, have been used to identify horizontal gene transfer events [8] and other reticulate phylogenetic relationships [3]. Genome similarity networks are typically constructed at different stringency thresholds (e.g. 50, 60, 70,

Funding: EL is supported by a Natural Sciences and Engineering Research Council (NSERC) scholarship. VM and FJL respectively hold NSERC discovery grants OGP0155251 and OGP249644. EB is funded by the European Research Council under the European Community's Seventh Framework Program FP7 (Grant Agreement n ${ }^{\circ} 615274$ ).
Competing Interests: The authors have declared that no competing interests exist.
$90,99 \%$ ) [6], or by using constantly increasing datasets, thus producing a range of inclusive networks. Such a strategy allows the detection of ancient evolutionary connections [1] or the verification of ecological distribution of taxa [9]. Furthermore, network analysis can be used with heterogeneous types of biological data, e.g. for linking protein structures to their functions [10,11].

Previous works in this field have focused on the use of conventional graph-theoretic measures describing the evolution of networks, such as the numbers of nearest neighbors or certain network motifs [12,13], or the distribution of shortest paths [9]. In this study, we present a number of novel features, which characterize evolving networks. All of them are based on the presence of additional nodes and edges in the augmented network. These added nodes and edges can be used to connect the original network nodes through different types of simple paths (i.e. loopless paths or paths that do not visit the same nodes twice) [14,15]. Precisely, we will describe a new polynomial time algorithm for estimating the number of Breakthroughs, Roadblocks, Impasses, Detours, Equal paths and Shortcuts (BRIDES) in evolving networks. Moreover, we have developed $\mathrm{C}++$ and R functions implementing the new algorithm. We will also present the results of our simulation study comparing the performances of four different versions of our algorithm as well as the application of the most successful version of BRIDES to real genome similarity networks. It is worth noting that, contrary to previous work, we were neither interested in counting the number of colored motifs in networks [16], nor in determining their types [12, 13].

## Materials and Methods

## Description of the BRIDES algorithm

This section describes the problem we address here from a mathematical point of view and presents the most important computational details of our algorithm. The main questions that we try to answer in this paper are the following:

1. Is there a simple path between two given nodes $i$ and $j$ (i.e. original network nodes in our study) that contains at least one node from a specific set of nodes (i.e. set of added nodes in our study)?
2. If such a simple path exists, is it the shortest path between $i$ and $j$ ?

Since the number of simple paths between two given nodes in a graph can be exponential in the size of the graph, visiting and counting all of them is a problem belonging to \#P [14, 17]. On the other hand, the number of simple shortest paths between two nodes of an undirected graph can also be exponential in the number of the graph nodes. Furthermore, the problem of finding a simple shortest path including a set of must-include nodes is NP-hard [18, 19]. Therefore, effective heuristic algorithms should be applied to answer questions (a) and (b), especially when large genetic or genomic similarity networks are considered. Vardhan and colleagues [19] proposed a fast heuristic algorithm to compute a simple path that contains a given ordered set of must-include nodes. However, this problem is slightly different from our problem, since our main objective is to find a shortest simple path including at least one node from a set of specified nodes. Li and colleagues [20] tried to address the latter problem, presenting a fast heuristic approach based on the principle of optimality of dynamic programming. However, their elegant algorithm can be applied only to graphs with a specific-series/parallel-topology [20].

The BRIDES algorithm takes as input two networks: (1) network $X$ with an original set of nodes $N_{X}$ and edges $E_{X}$ (Fig 1A) and (2) network $Y$ with an augmented set of nodes $N_{Y}$ and edges $E_{Y}$ (Fig 1B). All nodes of network $X$ should also be present in network $Y$ (i.e. $N_{X} \subset N_{Y}$ ).


Fig 1. Examples of the BRIDES (Breakthrough, Roadblock, Impasse, Detour, Equal and Shortcut) paths in evolving networks. Panel (A) presents an original network $X$ with 12 nodes. Panel (B) presents an augmented network $Y$ with 15 nodes (including 12 original and 3 added nodes, which are colored in grey). Six different types of paths are shown in the augmented network $Y$.
doi:10.1371/journal.pone.0161474.g001
However, it is not required that $E_{X} \subset E_{Y .}$. We first compute the shortest paths between the pairs of nodes in $X$, and then reassess their length in $Y$, by forcing these paths to include at least one added node (i.e. a node present in $Y$, but not in $X$ ). Our heuristic relies on a repeated application of Dijkstra's algorithm [21] to evaluate the impact of added nodes to the length of the shortest paths between the original nodes (see Algorithm 1).

Now we can define six distinct types of paths, related to the existence of added nodes in $Y$, which can be used to characterize complex relationships in evolving networks (Fig 1):

Breakthrough: a path that is impossible in network $X$ but is possible in network $Y$ (e.g. path between nodes 2 and 12, passing by added node 15 in Fig 1B);

Roadblock: a path that is possible in network $X$ but is impossible in network $Y$ (e.g. a simple path between nodes 4 and 7 that passes by an added node in $Y$ is impossible, see Fig 1B);

Impasse: a path that is impossible in both networks, $X$ and $Y$ (e.g. there are no possible paths between nodes 9 and 11 in Fig 1A and 1B);

Detour: a path that is shorter in network $X$ than in network $Y$ (e.g. path between nodes 1 and 3 in Fig 1A and 1B);

Equal: a path that has the same length in networks $X$ and $Y$ (e.g. path between nodes 1 and 6, assuming that all edge lengths in $X$ and $Y$ are equal, Fig 1A and 1B);

Shortcut: a path that is longer in network $X$ than in network $Y$ (e.g. path between nodes 2 and 8 in Fig 1A and 1B).

Fig 2 provides an example of computation of the BRIDES statistics in evolving networks. We can see that the addition of new nodes and edges to an evolving network can substantially change the distribution of the six types of paths defined in our study. The four heuristic strategies tested in our simulations, called BRIDES (the original strategy), BRIDES_Y, BRIDES_YC and BRIDES_EC, are presented in details in Algorithm 1 below:

## Algorithm 1

Given an original undirected network $\mathrm{X}=\left(\mathrm{E}_{\mathrm{X}}, \mathrm{N}_{\mathrm{X}}\right)$ and its augmented undirected network $Y=\left(E_{Y}, N_{Y}\right)$, i.e. network such that $N_{X} \subset N_{Y}$, this algorithm calculates the number of Breakthroughs, Roadblocks, Impasses, Detours, Equal paths and Shortcuts (BRIDES) to characterize the evolution of X into Y .

## BRIDES

Step 1. Compute the length of the shortest path between all pairs of nodes in network $X$. Find at most MaxPathNumber of simple shortest paths between pairs of original nodes (i,j), (i.e. nodes such that $i \in N_{X}$ and $j$ $\in N_{X}$ ) in network Y, using Dijkstra'salgorithm. Store in the list $P_{i j}$ the set of simple shortest paths corresponding to a pair of original nodes (i,j) in network Y.
Step 2. For all pairs of original nodes $(i, j)$, create a list $L_{i j}$ of added nodes $k\left(k \in N_{Y}, k \notin N_{X}\right)$ ordered with respect to the closeness of $i$ and $j$ to $k$. Calculate the distances $d(i, k)$ and $d(j, k)$ in Yusing Dijkstra and store at most MaxPathNumber of simple shortest paths in $P_{i k}$ and $P_{j k}$, respectively. Order the list of added nodes $L_{i j}$ according to either the minimum of $\operatorname{Max}(d(i, k), d(j, k))$ (Strategy 1 that provided better overall results in our simulations; the results of this strategy will be presented in the next section) or the minimum of $(d(i, k)+d(j, k))$
(Strategy 2). In order to speed up the algorithm, we can reduce the size of $L_{i j}$ by using the input parameters: MaxDistance (the maximum allowed distance from $i$ or from $j$ to $k$ ) and/or MaxNode (the maximum number of added nodes, $k$, in this list).
Set the first pair of original nodes (i,j) as the current pair of nodes.
Step 3. Do, for the current pair of original nodes (i,j):
If there exists a simple path in $P_{i j}$ that includes at least one added node, update the BRIDES statistics (see Table 1) with the results obtained for the current pair of nodes ( $i, j$ ), set the next pair ( $i, j$ ) as the current pair of original nodes and go to the beginning of Step 3; otherwise, go to Step 4.
Step 4. At this point, we have determined that the current pair of original nodes ( $i, j$ ) is not associated with a Breakthrough, Impasse or Shortcut, and we can now determine whether it should be associated with a Detour, Equal path or Roadblock.
Do, for each node $k$ of the ordered list $L_{i j}$, starting from the firstelement of $L_{i j}$ :
Step 4.1. If the concatenation of paths [ $i, k]$ from $P_{i k}$ and $[j, k]$ from $P_{j k}$ is a simple path, set $d(i, j)=d(i, k)+d(j, k)$ and update the BRIDES statistics (see Table 1) with the results obtained for the pair of nodes (i, $j$ ), set the next pair ( $i, j$ ) as the current pair of original nodes and go to Step 3; otherwise, go to Step 4.2.
Step 4.2. Since there are repeating nodes, except $k$, on the paths [ $i, k$ ] and $[j, k]$, temporarily remove them from network $Y$ and recalculate: (1) the shortest path from j to $k$ in the reduced network Yusing Dijkstra, storing the result in $P_{j k}$, and (2) the shortest path from $i$ to $k$ in the reduced network Yusing Dijkstra, storing the result in $P_{i k}$. Repeat

Step 4.1 with the shortest of concatenations of two paths stored: (1) in $P_{i k}$ and $P_{j k}^{\prime}$ and (2) in $P_{j k}$ and $P_{i k}$ '; if for both $P_{j k}$ ' and $P_{i k}$ ' does not return a simple shortest path because no such path exists in the reduced network $Y$, consider the next node $k$ of $L_{i j}$ in Step 4.1 or go to Step 5 if all element of $L_{i j}$ have been already examined.
Step 5. Classify the path associated with the current pair of nodes (i, j) as a Roadblock.

Step 6. If all the pairs ( $i, j$ ) have been already examined, print the BRIDES statistics; otherwise, set the next pair (i,j) as the current pair of original nodes and go to Step 3
Heuristic BRIDES_Y (BRIDES using Yen's algorithm)
Replace Steps 3 and 4 above by the following steps:
Step 3'. Do, for the current pair of original nodes (i,j):
Compute the ordered list $P Y_{i j}$ of MaxPathNumber shortest paths between $i$ and jusing Yen's k-shortest path algorithm [ 22] .
Step $4^{\prime}$. Do, for each path pof the ordered list $P Y_{i j}$,
If $p$ contains at least one added node, update the BRIDES statistics (see Table 1) with the results obtained for the current pair of original nodes (i,j), set the next pair (i,j) as the current pair of original nodes and go to Step 3 .
Heuristic BRIDES_YC (BRIDES using Yen's algorithm and Concatenation of paths)
Replace Steps 2 and 4 above by the following steps:
Step 2 '. For all pairs of original nodes (i,j), create alist $L_{i j}$ of added nodes $k$ ( $k \in N_{Y}, k \notin N_{X}$ ) ordered with respect to the closeness of $i$ and $j$ to $k$. Calculate the distances $d(i, k)$ and $d(j, k)$ in Yusing Dijkstra. Order the list of added nodes $L_{i j}$ according to the minimum of $\operatorname{Max}(d(i, k), d(j$, k) ) (Strategy 1) or the minimum of (d(i,k) +d(j,k)) (Strategy 2). Using Yen's algorithm compute and store at most MaxPathNumber of paths in $P_{i k}$ and $P_{j k}$, respectively. In order to speed up the algorithm, we can reduce the size of $L_{i j}$ by using the input parameters: MaxDistance and/or MaxNode.
Set the first pair of original nodes (i,j) as the current pair of nodes.
Step 4'. Do, for each node $k$ of the ordered list $L_{i j}$, starting from the first element of $L_{i j}$ :
Step 4.1. If the concatenation of paths [ $i, k]$ from $P_{i k}$ and $[j, k]$ from $P_{j k}$ is a simple path, set $d(i, j)=d(i, k)+d(j, k)$ and update the BRIDES statistics (see Table 1) with the results obtained for the pair of nodes (i, $j)$, set the next pair ( $i, j$ ) as the current pair of original nodes and go to Step 3.
Go to Step 5 if all element of $L_{i j}$ have been already examined.
BRIDES_EC (BRIDES algorithm based on an Exhaustive Concatenation approach)
The difference with the original BRIDES algorithm is in Step 4, where we examine all the nodes $k$ of the ordered list $L_{i j}$, even though a simple path has been found in Step 4.1.

The default values of the parameters MaxPathNumber, MaxDistance and MaxNode in our program are all equal to 100 . These default values were also used in our simulation study (see the next section). It is worth noting that in unweighted graphs, MaxDistance represents the upper bound of the number of edges on the path between an original and an added node. Obviously, in weighted graphs, this parameter should be specified by the user. The time complexity of Steps 1 and 2 of our original BRIDES algorithm is $O\left(\left|N_{X}\right| \times \operatorname{MaxPathNumber} \times\left(\left|E_{Y}\right|+\left|N_{Y}\right|\right.\right.$


Fig 2. Computation of the BRIDES statistics in evolving networks. Addition of the new nodes (colored in grey) and edges to an evolving network changes the distribution of different types of network pathways as time ( $T$ ) progresses. The letters B, R, I, D, E and S at the bottom of the chart stand respectively for Breakthroughs, Roadblocks, Impasses, Detours, Equal paths and Shortcuts.
doi:10.1371/journal.pone.0161474.g002

Table 1. Possible BRIDES outcomes depending on the path type identified by the algorithm.

| Simple path between $\boldsymbol{i}$ to $\boldsymbol{j}$ in $\boldsymbol{X}$ | Simple path between $\boldsymbol{i}$ to $\boldsymbol{j}$ in $\boldsymbol{Y}$ | BRIDES statistic |
| :--- | :--- | :--- |
| Impossible | Possible | Breakthrough |
| Possible | Impossible | Roadblock |
| Impossible | Impossible | Impasse |
| Shorter distance | Longer distance | Detour |
| Equal distance | Equal distance | Equal |
| Longer distance | Shorter distance | Shortcut |

doi:10.1371/journal.pone.0161474.t001
$\left.\log \left(\left|N_{Y}\right|\right)\right)$, using asymptotically the fastest known single-source shortest-path version of Dijkstra's algorithm, where $\left|N_{X}\right|$ and $\left|N_{Y}\right|$ are the numbers of nodes in networks $X$ and $Y$, respectively, and $\left|E_{Y}\right|$ is the number of edges in network $Y$. The time complexity of Step 4 is $O\left(\left|N_{X}\right|^{2} \times\right.$ MaxNodes $\times\left(\left|E_{Y}\right|+\left|N_{Y}\right| \log \left(\left|N_{Y}\right|\right)\right)$, in the worst case. However, in practice, the runtime of this step is much lower because we rarely execute the internal loop of Step 4 all the MaxNodes times. This leads to the total time complexity of BRIDES equal to $O\left(\left|N_{X}\right| \times(\right.$ MaxPathNumber + $\left|N_{X}\right| \times$ MaxNodes $) \times\left(\left|E_{Y}\right|+\left|N_{Y}\right| \log \left(\left|N_{Y}\right|\right)\right)$. The presented BRIDES algorithm can be applied to analyze undirected graphs with non-negative edge lengths. When negative edge lengths exist in either network $X$ or network $Y$, the improved version of Bellman-Ford's algorithm [23] could be applied instead of Dijkstra.

We created an R function implementing the BRIDES algorithm using the graph manipulation tools available in the igraph package [24]. The R version of BRIDES can be applied for the analysis of small networks ( $<1,000$ nodes). For larger networks ( $>1,000$ nodes), we recommend using the

C++ version of our program, which includes all the four heuristic algorithms, BRIDES, BRIDES_Y, BRIDES_YC and BRIDES_EC, discussed in this paper. Moreover, a parallel OpenMP [25] version of the C++ program is also available (see: https://github.com/etiennelord/BRIDES).

## Results

## Simulation study

To test the BRIDES algorithm, we carried out a simulation study using three popular network models implemented in the igraph package (version 1.0.0) [24]. Precisely, the Erdős-Rényi [26], Barabási-Albert [27] and Watts-Strogatz [28] random graph generation models were considered. The Barabási-Albert model is a well-known approach for generating scale-free (or powerlaw) networks, while the Erdős-Rényi and Watts-Strogatz models are among the most popular generation models for random graphs that do not exhibit a scale-free degree distribution.

Using each of these three models, we generated 1000 random original networks $X$ with 100 nodes, and then added to them $5,25,50$ or 100 additional nodes to create augmented networks Y. The simulations were performed using the C++ version of our program executed on a PC computer equipped with an Intel i7-3770 CPU $(3.40 \mathrm{GHz})$ and 8 Gb of RAM. The four competing heuristic strategies, BRIDES, BRIDES_Y, BRIDES_YC and BRIDES_EC, presented in Algorithm 1 were tested in our simulation study. The accuracy of the competing approaches (see Fig 3A) was calculated as the percentage of correctly labeled path types (i.e. the percentage of true positive Breakthroughs, Roadblocks, Impasses, Detours, Equal paths and Shortcuts) provided by each heuristic. The identification of the correct (i.e. reference) path types was carried out using a brute force procedure based on a depth-first search (DSF) algorithm. Along with the average accuracy, calculated over all generated graphs, we also measured the average runtime (in seconds; see Fig 3B and S1 Table) of each of the four heuristics under comparison.

The results of our simulations suggest that the original BRIDES strategy along with the exhaustive concatenation procedure, BRIDES_EC, were able to provide the correct classification of paths, regardless of the number (i.e. also percentage, in this case) of added nodes (Fig 3A). The two heuristics based on Yen's $k$-shortest path algorithm (i.e. BRIDES_Y and BRIDES_YC), returned the correct classification of paths in $67 \%$ and $90 \%$ of cases, respectively, when the number of added nodes was 5 . However, the results obtained with BRIDES_Y and BRIDES_YC improved with an increase of the number of added nodes, reaching the accuracy level of $100 \%$ for 100 added nodes.

The original BRIDES algorithm was the fastest among the four compared heuristics regardless the number of added nodes (Fig 3B). The worst performance, in terms of running time, was shown by BRIDES_Y, for small numbers of added nodes. This can be explained as follows. On one hand, we restrict our search in Yen's algorithm to only 100 shortest paths. On the other hand, when the proportion of added nodes in $Y$ is very small, all of them can be located far away from both source and destination nodes given as input to Yen's algorithm. Thus, these rare added nodes can never be included in the set of 100 shortest paths returned by BRIDES_Y. This leads to an important decrease in accuracy (Fig 3A) and increase in computational time (Fig 3B). The heuristic BRIDES_YC, which uses both Yen's algorithm and concatenation of paths, performs better in this case since the concatenated paths are guaranteed to contain at least one added node.

It is worth noting that the length of a Detour path identified by the BRIDES algorithm can be longer than the length of the shortest possible Detour existing in the network, but in this work, we are only interested in estimating the distribution of path types, and not in assessing the exact path lengths.



Fig 3. The average accuracy $(A)$ and computational time $(B)$ obtained for the four heuristic strategies, BRIDES, BRIDES_Y, BRIDES_YC and BRIDES_EC, presented in our study. The simulations were carried out with original networks $X$ containing 100 nodes and generated using the Erdős-Rényi, BarabásiAlbert and Watts-Strogatz random graph generation models. The augmented networks $Y$ contained 5, 25, 50 or 100 added nodes and all original nodes of $X$. 1000 graphs were generated for each parameter configuration.
doi:10.1371/journal.pone.0161474.g003


Fig 4. BRIDES statistics for real genome similarity networks at $\mathbf{9 0 \%}$ similarity threshold. The BRIDES statistics (A) computed for the original network $X$ comprising archaea (in red) and bacteria (in green), 326 species in total, and the four augmented similarity networks $Y$ (the added nodes are in blue), including: (B) photosynthetic eukaryotes, (C) nonphotosynthetic eukaryotes, (D) plasmids and (E) viruses.

Table 2. General network and BRIDES statistics for the four real genome similarity networks presented in Fig 4.

|  | General network statistics |  |  |  |  | BRIDES statistics $^{\mathbf{a}}$ |  |  |  |  |  |
| :--- | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| Added species | Total of <br> nodes | Total of <br> edges | Average <br> degree | Average path <br> length | Clustering <br> coefficient | $\mathbf{B}$ | $\mathbf{R}$ | I | D | E | S |
| Eukaryotes photosynt. | 345 | 2,014 | 11.68 | 5.97 | 0.867 | 1,652 | 3,329 | 42,418 | 5,550 | 19 | 7 |
| Eukaryotes <br> nonphotosynt. | 345 | 1,845 | 10.70 | 5.29 | 0.865 | 0 | 8,905 | 44,070 | 0 | 0 | 0 |
| Plasmids | 3,848 | 187,848 | 97.63 | 2.90 | 0.559 | 23,618 | 7,057 | 20,452 | 689 | 185 | 974 |
| Viruses | 1,984 | 12,054 | 12.15 | 5.23 | 0.801 | 0 | 8,577 | 44,070 | 328 | 0 | 0 |

${ }^{\text {a }}$ Computation were carried out using the following input parameters: MaxDistance $=100$, MaxNode $=100$ and MaxPathNumber $=100$.
doi:10.1371/journal.pone.0161474.t002

## Application of BRIDES to real biological data

To evaluate the performance of the BRIDES algorithm and calculate the related statistics (Fig 4A) for real networks, we generated four genome similarity networks using a set of 2,094,593 nucleotide sequences of archaea, bacteria, photosynthetic and nonphotosynthetic eukaryotes, plasmids and viruses. Similarity between the nucleotide sequences was determined using $B L A S T$ [29] with a minimum $e$-value of $10 e$ - 5 . Individual genomes were connected in both original and augmented networks if at least one of their genes shared a homologous sequence ( $>70 \%$ cover, with the $90 \%$ similarity threshold). A total of 326 prokaryotes were selected to form the original network $X$, and then complemented with either photosynthetic eukaryotes (Fig 4B), or nonphotosynthetic eukaryotes (Fig 4C), or plasmids (Fig 4D), or viruses (Fig 4E) in the augmented network $Y$.

The BRIDES statistics provided by our algorithm for the four genome similarity networks exhibited different distribution profiles (Fig 4A). Even when the genome networks displayed similar clustering coefficients and comparable average path lengths (Table 2), the BRIDES statistics could be quite different (Fig 4A). For example, the addition of photosynthetic eukaryotes resulted in a large number of Detours, Shortcuts and Equal paths (Fig 4B), whereas the addition of nonphotosynthetic eukaryotes resulted in the complete disappearance of such path types (Fig 4C). This difference can be explained by the fact that nuclear genomes of photosynthetic eukaryotes host gene families from cyanobacterial origin, as a result of gene transfer from their chloroplastic endosymbionts, which are typically absent in nonphotosynthetic eukaryotes. Moreover, the addition of 3552 plasmids (Fig 4D) to the original network $X$ led to a similar BRIDES profile as in the case of photosynthetic eukaryotes, while favouring the emergence of Shortcuts. On the contrary, the addition of viruses (Fig 4E) did not introduce any Shortcuts into the augmented similarity network, but led to the increase of the numbers of Roadblocks. The latter result is consistent with findings of Halary and colleagues [8], who identified plasmids as central genetic carriers across prokaryotic genomes, whereas viruses were found to have restricted host ranges for infecting distantly related taxa.

## Conclusion

In this paper, we introduced a new fast algorithm and associated software for characterizing different types of paths existing in evolving similarity networks. In particular, our algorithm calculates the number of Breakthroughs, Roadblocks, Impasses, Detours, Equal paths and Shortcuts (BRIDES), which can be present in these networks. Our program, implemented in the C++ and R programming languages, includes four heuristic algorithms for calculating the BRIDES statistics discussed and compared in our study (see Algorithm 1). These statistics can be viewed as a new tool for the characterization and comparison of evolving genome and gene
similarity networks, transcriptional networks [30] or interactome networks [31]. The analysis and comparison of evolving networks can be carried out for different network stringency thresholds. Dijkstra's algorithm used in our method makes it suitable for the analysis of both weighted and unweighted types of networks. Note that our BRIDES heuristic presented here in the case of undirected networks can be easily adapted to the case of directed networks. In the future, it would be interesting to see whether the Uniform Cost Search [32] or A* [33,34] algorithms can be used as an alternative of Dijkstra in order to accelerate the computation of the BRIDES statistics within our method.

## Dataset and Source Files

The R and C++ source codes are available from the Github repository (https://github.com/ etiennelord/BRIDES/) with a GPL version 3 license. The sample networks (Figs 1 and 2) are located in either the R or C++ source directories. The source code for the simulations (Fig 3) is located in the Simulation directory of the github repository. The genome similarity networks (Fig 4, Table 2) are available in the GenomeNetwork directory.

## Supporting Information

S1 Table. Average computational time in seconds (s) obtained for the four heuristics and for different network models. The original network $X$ contained 100 nodes and the augmented networks $Y$ contained 5, 25, 50 or 100 added nodes. For each model, 1000 networks were created, and 100 path were randomly selected for evaluation. The reported values are average time (in seconds) for the evaluation of each path.
(PDF)

## Acknowledgments

We thank Dr. Philippe Lopez for critical discussion on genome similarity networks.

## Author Contributions

Conceptualization: EL EB FJL.
Data curation: EL RM.
Formal analysis: EL FJL.
Funding acquisition: EB VM FJL.
Investigation: EL MLC RM.
Methodology: EL MLC EB VM FJL.
Project administration: FJL.
Software: EL MLC RM VM.
Supervision: FJL.
Validation: EL EB FJL.
Visualization: EL.
Writing - original draft: EL MLC FJL.
Writing - review \& editing: EL EB VM FJL.

## References

1. Cheng S, Karkar S, Bapteste E, Yee N, Falkowski P, Bhattacharya D. Sequence similarity network reveals the imprints of major diversification events in the evolution of microbial life. Front Ecol Evol. 2014; 2: 1-13.
2. Orsini C, Dankulov MM, Colomer-de-Simón P, Jamakovic A, Mahadevan P, Vahdat A, et al. Quantifying randomness in real networks. Nat Commun. 2015; 6: 8627. doi: 10.1038/ncomms9627 PMID: 26482121
3. Lynch MD, Bartram AK, Neufeld JD. Targeted recovery of novel phylogenetic diversity from next-generation sequence data. ISME J. 2012; 6: 2067-2077. doi: 10.1038/ismej.2012.50 PMID: 22791239
4. Wuchty S, Uetz P. Protein-protein interaction networks of E. coli and S. cerevisiae are similar. Sci Rep. 2014; 4: 7187. doi: 10.1038/srep07187 PMID: 25431098
5. Montoya JM, Pimm SL, Solé RV. Ecological networks and their fragility. Nature. 2006; 442: 259-264. PMID: 16855581
6. Popa O, Hazkani-Covo E, Landan G, Martin W, Dagan T. Directed networks reveal genomic barriers and DNA repair bypasses to lateral gene transfer among prokaryotes. Genome Res. 2011; 21: 599609. doi: 10.1101/gr.115592.110 PMID: 21270172
7. Vidal M, Cusick ME, Barabási AL. Interactome networks and human disease. Cell. 2011; 144: 986998. doi: 10.1016/j.cell.2011.02.016 PMID: 21414488
8. Halary S, Leigh JW, Cheaib B, Lopez P, Bapteste E. Network analyses structure genetic diversity in independent genetic worlds. Proc Natl Acad Sci USA. 2010; 107: 127-132. doi: 10.1073/pnas. 0908978107 PMID: 20007769
9. Forster D, Bittner L, Karkar S, Dunthorn M, Romac S, Audic S, et al. Testing ecological theories with sequence similarity networks: marine ciliates exhibit similar geographic dispersal patterns as multicellular organisms. BMC Biol. 2015; 13: 16. doi: 10.1186/s12915-015-0125-5 PMID: 25762112
10. Atkinson HJ, Morris JH, Ferrin TE, Babbitt PC. Using sequence similarity networks for visualization of relationships across diverse protein superfamilies. PloS ONE. 2009; 4: e4345. doi: 10.1371/journal. pone. 0004345 PMID: 19190775
11. Wang B, Mezlini AM, Demir F, Fiume M, Tu Z, Brudno M, et al. Similarity network fusion for aggregating data types on a genomic scale. Nat Methods. 2014; 11: 333-337. doi: 10.1038/nmeth. 2810 PMID: 24464287
12. Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U. Network motifs: simple building blocks of complex networks. Science. 2002; 298: 824-827. PMID: 12399590
13. Bapteste E, van lersel L, Janke A, Kelchner S, Kelk S, McInerney JO, et al. Networks: expanding evolutionary thinking. Trends Genet. 2013; 29: 439-441. doi: 10.1016/j.tig.2013.05.007 PMID: 23764187
14. Roberts B. Kroese DP. Estimating the number of s-t paths in a graph. J Graph Algorithms Appl. 2007; 11: 195-214.
15. Martins EQ. Pascoal MM. A new implementation of Yen's ranking loopless paths algorithm. 4OR-Q J Oper Res. 2003; 1: 121-133.
16. Schbath S, Lacroix V, Sagot MF. Assessing the exceptionality of coloured motifs in networks. EURASIP J Bioinform Syst Biol. 2009; 1; 616234 .
17. Valiant LG. The complexity of enumeration and reliability problems. SIAM J Comput. 1979; 8: 410-421.
18. Burkard RE, Deineko VG, van Dal R, van der Veen JA, Woeginger GJ. Well-solvable special cases of the traveling salesman problem: a survey. SIAM Rev. 1998; 40: 496-546.
19. Vardhan H, Billenahalli S, Huang W, Razo M, Sivasankaran A, Tang L, et al. Finding a simple path with multiple must-include nodes. IEEE MASCOTS. 2009;1-3.
20. Li WJ, Tsao HSJ, Ulular O. The shortest path with at most/nodes in each of the series/parallel clusters. Networks. 1995; 26: 263-271.
21. Dijkstra EW. A note on two problems in connexion with graphs. Numer Math. 1959; 1:269-271.
22. Yen JY. An algorithm for finding shortest routes from all source nodes to a given destination in general networks. Q Appl Math. 1970; 27: 526-530.
23. Goldberg AV, Radzik TA. Heuristic improvement of the Bellman-Ford algorithm. Appl Math Lett.1993; 6: 3-6.
24. Csardi G, Nepusz T. The igraph software package for complex network research. Inter J Complex Syst. 2006; 1695: 1-9.
25. OpenMP Forum. Openmp: A proposed industry standard api for shared memory programming. Technical report, Oct. 1997
26. Erdős P, Rényi A. On random graphs. Pub Math Debrecen. 1959; 6: 290-297.
27. Barabási AL, Albert R. Emergence of scaling in random networks. Science. 1999; 286: 509-512. PMID: 10521342
28. Watts DJ, Strogatz SH. Collective dynamics of ‘small world’ networks. Nature 1998; 393: 440-442. PMID: 9623998
29. Altschul SF, Gish W, Miller W, Myers EW, Lipman DJ. Basic local alignment search tool. J Mol Biol. 1990; 215: 403-410. PMID: 2231712
30. Aylwarda FO, Eppleya JM, Smithb JM, Chavezb FP, Scholinb CA, DeLong EF. Microbial community transcriptional networks are conserved in three domains at ocean basin scales. Proc Natl Acad Sci USA. 2015; 112: 5443-5448. doi: 10.1073/pnas. 1502883112 PMID: 25775583
31. Menche J, Sharma A, Kitsak M, Ghiassian SD, Vidal M, Loscalzo J, et al. Uncovering disease-disease relationships through the incomplete interactome. Science. 2015; 347: 1257601. doi: 10.1126/science. 1257601 PMID: 25700523
32. Verwer BJH, Verbeek PW, Dekker ST. An efficient uniform cost algorithm applied to distance transforms. IEEE Trans Pattern Anal Mach Intell. 1989; 4: 425-429.
33. Hart PE, Nilsson NJ, Raphael B. A formal basis for the heuristic determination of minimum cost paths. IEEE Trans Syst Sci Cybernetics. 1968; 4: 100-107.
34. Zeng W, Church RL. Finding shortest paths on real road networks: the case for A*. Int J Geogr Inf Sci. 2009; 23: 531-543.
