Topologically Inspired Walks on Randomly Connected Landscapes With Correlated Fitness

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Strictly adaptive walks on uncorrelated and correlated fitness landscapes have been a subject of intense research. However, some experimental findings tend to advance the notion of non-adaptive evolution in terms of epistasis. To address such evolutionary paths, herein we introduce the concept of topologically inspired walks on connected and correlated landscapes with complex topologies. These walks are dictated solely by the topology of connections and are not explicitly dependent on the underlying fitness values. In the biologically significant regime of sparse randomness, we observe that such topologically inspired walks might carry a population to a local optimum even faster than strictly adaptive walks. This effect becomes more pronounced with increasing correlations in fitness. We observe interesting tradeoffs between topologically inspired walks governed by the minimum and maximum value of a set of given network metrics.

1. INTRODUCTION

The notion of fitness landscapes variously referred to as "adaptive topographies", "adaptive landscapes", and "surfaces of selective value", have been extensively used to model the process of evolution [1–5]. Recently, there has been a surge of theoretical and experimental activity in this area [6–24] attesting to its immense importance.

Originally, fitness landscapes were conceived of as a genotype space represented on a hypercube [1]. Thus, each genotype is a sequence configuration with assigned fitness value and has the same number of neighbors. Fitness landscapes intend to relate either an individual's fitness with its genotype or the genetic state of the population with its allele frequency. Evolution on a fitness landscape is visualized as movement of the state of a population or an individual over the genotype space due to mutation, natural selection etc. [23]. Notably, fitness landscapes are also used for modeling evolution of a specific nucleotide sequence (DNA or RNA), gene sequence or protein [6, 8, 24–27]. In fitness landscapes with a single smooth peak, all mutations along any evolutionary path result in an increase in fitness. Strictly adaptive walks in the original hypercubic model is visualized as a movement from one genotype toward a neighboring genotype of higher fitness, differing merely by a single mutation [2, 3, 5]. The walk continues as long as a beneficial mutation is available [11].

However, experimentally observed fitness landscapes possess complexities which are not captured by simple models. They can be rather rugged, with a number of local peaks which are surrounded by valleys. Evolutionary walks on rugged fitness landscapes have been modeled as different types of adaptive walks [2, 3]. In random adaptive walks (RAW), a neighboring genotype with higher fitness is selected randomly. In gradient or greedy adaptive walks (GAW), the neighbor

with the highest fitness value is selected. These walks are expected to take the population to a local optimum in the multi-peaked fitness landscape. Of prime interest is the mean walk length of evolutionary walks that will eventually lead to a local optimum in the fitness landscape [3, 4].

2. VARIOUS PATHS SUGGESTED BY EXPERIMENTAL EVOLUTION

Adaptive walks have proved as a great starting point to model evolution. However, apart from adaptive walks, experimental evidence suggests that non-adaptive evolutionary paths could also exist [28–31]. The central idea responsible for the emergence of ruggedness in fitness landscape is the idea of epistatic interactions where the expression of one gene is affected by another gene at a different locus [28]. These interactions are well known in evolution and have been thoroughly studied in experiments. An interesting case of such epistatic interactions is reciprocal sign epistasis where the occurrence of two deleterious mutations result in an increment of fitness [24].

Various experimental studies support such non-adaptive evolutionary paths. It was observed in *E. coli* [30] and *S. typhimurium* [31] that mutations responsible for streptomycin resistance cause a decrease in fitness where a compensatory second site mutation helps in increasing the overall fitness due to epistatic interaction. The same phenomenon of decrease in fitness in an evolutionary path is also observed in experiments on lac operon [29]. In *in vivo* experiments with TEM-1 β-lactamase, it was observed that the evolutionary path toward a resistant mutant of higher fitness went through lower fitness due to decrease of stability [9, 24].

All these studies indicate that a decrease of fitness in an evolutionary path is entirely possible, which however is not allowed by up-hill climbing walks. Our primary motive is to model an alternative evolutionary walk which can pass through not just fitness hills but also fitness valleys in a rugged fitness landscape as represented in Path "a" of **Figure 1**. Results from extensive numerical simulations show that our proposed walks indeed successfully capture this phenomenon and are non-adaptive in nature.

There also exist studies suggesting heterogeneous connectivity in a fitness landscape. Simultaneous multiple mutations are also observed in certain experiments [32] which suggest evolutionary walks similar to that represented by Path "b" of **Figure 1**. Such paths arise due to long range connections in the landscape with heterogeneous connectivity, unlike landscapes with hyper-cubic structure.

It is observed that many point mutations are responsible for the lethality of an individual [28, 33–36]. These lethal genotypes are not connected with other viable genotypes through an evolutionary path due to natural selection [4, 5, 37]. This results in isolated genotypes as represented in Path "c" of **Figure 1**, and also contributes to the heterogeneous connectivity in a fitness landscape.

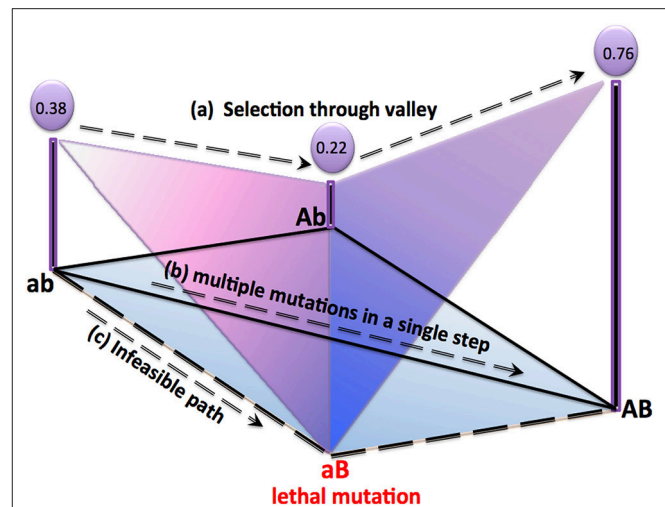It should be noted that fitness landscapes may not be uncorrelated as suggested by some studies on RNA [26, 27]

FIGURE 1 | Experimentally observed yet lesser studied paths for a 2-string genotype are shown in above representation of a realistic fitness landscape. All possible mutations for a 2-string genotype can be represented as "*ab*," "*AB*," "*Ab*," and "*aB*." Here "*aB*" is presumed as lethal. Fitness value of each genotype resulting from epistatic interaction is also mentioned. Apart from well-known adaptive walks, three other possible evolutionary paths are: **(a)** Non-adaptive path passing through a valley "*ab*" → "*Ab*" → "*AB*" as studied in Poelwijk et al. [8] and Wang et al. [9], **(b)** multiple mutations in a single step as studied in Refs. [24, 32], and, **(c)** infeasible path leading to the lethal mutation "*aB*" [33]. Topologically inspired walks on fitness landscapes with heterogeneous connectivities can successfully model **(a)**, **(b)**, and **(c)**.

and bacterial system [38]. Our motive is to incorporate above mentioned phenomena in our model for the construction of the fitness landscape and evolutionary walks.

To summarize—recent studies and experiments [6, 24, 27, 28, 30–33, 38] show that evolutionary trajectories in realistic and correlated fitness landscapes may pass through fitness valleys due to epistatic interactions or through long-range connections due to multiple mutations in a single step. Also, lethal mutations would lead to infeasible paths. . The aforementioned scenarios are depicted in **Figure 1**. Path "a," which is a non-adaptive path, shows that uphill climbing might not always be favored due to complex epistatic interaction between genes. Path "b" shows that multiple mutations can be achieved even in a single step. Path "c" shows that lethal mutations would produce isolated genotypes.

3. NETWORKS AND TOPOLOGICALLY INSPIRED WALKS ON FITNESS LANDSCAPES

A major aspect of network science is the intricate role of topology, as quantified by various metrics [39–42], which plays a prime part in the characterization, design and functioning of such systems. However, while networks have been used in a variety of biological problems [43–48], they have seen only limited application [4, 5] in fitness landscapes and adaptive walks on them.

In this work, we propose a new class of walks, namely topologically inspired walks (TIW). TIW are directed by the

topology of the randomly connected fitness landscape and are not explicitly dependent on the underlying fitness values. In consonance with experiments [9, 24, 30, 31, 49]—TIW traverse not only fitness peaks but also fitness valleys, unlike strictly adaptive walks like RAW and GAW. Further, in the biologically significant regime of sparse random graphs [50], TIW can carry a population to a local optimum faster than GAW or RAW. We also find that correlations [4, 5, 26, 27, 38] in fitness landscapes have a profound effect over such walks.

To model TIW on fitness landscapes, we studied well known network metrics based upon which TIW can be performed, namely, degree, closeness and betweenness. We explain below, how these measures capture various important topological aspects of nodes in the network.

Degree, k, of node, i, in a network, $\mathcal{G}$, which does not possess any self-loop, is the total number of connections it has to other nodes in a given network. Thus, its distribution is likely to offer ques into the connectivity pattern of the network.

Closeness, C_i, of node i, is the reciprocal of the average distance of i to every other node, j, in a network, $\mathcal{G}$, of N nodes. Thus,

$$C_i = \frac{N-1}{\sum_j d_{ij}}, \tag{1}$$

where, d_{ij} is the shortest distance between nodes i and j. The shortest distance between two nodes in a network, i and j is the minimum number of edges which is required to be traversed in order to reach from node i to node j. As such, more than one shortest path may exist between two given nodes of a network. Closeness of a node signifies how easily a given node in a network is accessible from the other nodes in the network. In a star graph for example, a single edge is required to reach the central node. Whereas, any other node apart from the central node, will need at least two edges to reach from the rest of the nodes in the star graph. Obviously, nodes in graphs with predominantly chain like structures will typically possess the opposite behavior with regard to closeness.

Betweenness, B_k, of node, k, in $\mathcal{G}$ is a measure of the number of shortest paths passing through k in $\mathcal{G}$. Thus,

$$B_k = \sum_{i \neq k \neq j} \frac{\sigma_{ij}(k)}{\sigma_{ij}}, \tag{2}$$

where, σ_{ij} is the number of shortest paths in $\mathcal{G}$ between node, i, to node, j, and $\sigma_{ij}(k)$ the number of such paths between i and j, passing through k. Thus, betweenness centrality of a node quantifies its influence over the communication or information flow between all pairs of the nodes in a network.

In order to introduce heterogeneous connectivity in fitness landscapes as described in the above section, the topology of connections in the fitness landscape is modeled upon Erdös Rényi (ER) random graphs [4, 5]. It may be noted that a node refers to a mutation in the fitness landscape. Henceforth, we will use the terms node and mutation interchangeably. In ER graphs, every pair of nodes is randomly connected with probability, p, and the expected total number of connections therefore is $pN(N-1)/2$.

Thus, the mean connectivity z of the resulting graph is $z = p(N-1) \simeq pN$, for large N. The degree distribution of an ER network is approximated by a Poisson distribution in the limit $N \to \infty$ and is given by,

$$P(k) = \frac{e^{-z}z^k}{k!} \tag{3}$$

An Erdös Rényi network is generated with fixed number of nodes, N. Pairs of nodes are connected randomly with probability, p. For $z > 1$, a single giant component is most likely to appear in the network. Here, we consider only those nodes that are present in the giant component.

We then ascribe a fitness value $f_i = 1 + s_i$ to each node i in the giant component to define the fitness landscape. Here, s_i is the selective effect of the mutation i. Let us randomly choose a node, i, which can be referred to as the seed node. This seed node is then assigned a value, s_i, which is a random number drawn from an exponential distribution, $P(S_i) = \alpha e^{\alpha S_i}$, with mean $1/\alpha$. In the present context, the mean of this distribution represents the selection strength of beneficial mutations in the population. In accordance with earlier literature, we have set $\alpha = 20$ [4, 51] under the presumption of high influx of beneficial mutations [51–54]. Now, to assign correlations in the fitness landscape, the selective effect of s_j of the neighboring node is drawn from a distribution such that s_j is conditional on s_i of the seed node. Thus, each $\{s_j \mid j \in$ neighborhood, $\mathcal{H}$ of $i\}$ is drawn from a gaussian distribution having mean λs_i and variance $\sigma^2(1 - \lambda^2)$, according to bivariate Gaussian distribution as shown in Equation (4).

$$P(s_j|s_i) = \frac{1}{\sqrt{2\pi\sigma^2(1-\lambda^2)}} exp\left(-\frac{(s_j - \lambda s_i)^2}{2\sigma^2(1-\lambda^2)}\right) \tag{4}$$

Here, λ is a correlation parameter defined in $[0, 1]$ where $\lambda = 0$ corresponds to uncorrelated fitness landscape. We now repeat the same exercise for all neighbors of every member of $\{j \mid j \in \mathcal{H}\}$, which have not yet been assigned a fitness value. This process is conducted until all nodes in the network are assigned with a fitness value [4].

We consider TIW based on node degree, node betweenness, and node closeness [39–42] upon these networks. For a given metric, two types of walks were performed—min-directed TIW and max-directed TIW. A min-directed TIW starts from a randomly chosen non local optimum. The walk is then directed toward the neighboring node possessing minimum value of the network metric under consideration, among all neighbors. Similarly, a max-directed TIW starts from a randomly chosen non local optimum. The walk is then directed toward the neighboring node possessing the maximum value of the network metric under consideration, among all neighbors. The process is repeated until a local optimum is reached. To make the walks self-avoiding, if a neighbor possessing the minimum (or maximum) value of a given metric has already been traversed, the neighbor with the second lowest (or highest) value is selected to continue the walk. Thus, by definition, these walks are dictated by the topology of connections in the fitness landscape and are not
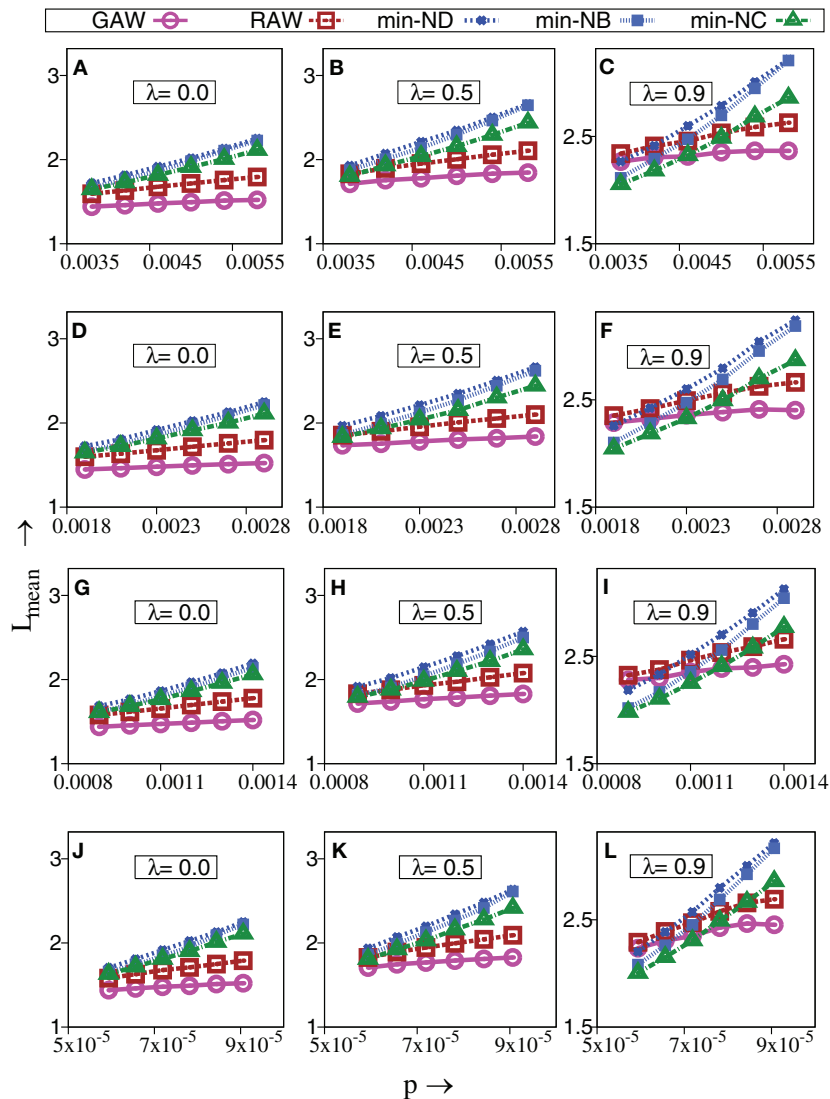
FIGURE 2 | Change in mean walk length of strictly adaptive walks (RAW, GAW) and topologically inspired walks (TIW) governed by minimum value of degree (*ND*), betweenness (*NB*) and closeness (*NC*) of nodes vs. probability of connections, *p*. The topology of the genotype space is based upon Erdös Rényi graphs. The fitness values are drawn from a bivariate Gaussian distribution having correlation parameter, λ and $\sigma^2 = 0.001$, $\alpha = 20$. **(A–I)** Are for a set of $N_E = 10^3$ networks, with 10^3 walks performed on each network of nodes $N = 512, 1024,$ and 2048, respectively, resulting in a total of 10^6 walks at a given value of *p*. **(J–L)** are for a set of $N_E = 500$ networks, with 10^3 walks performed on each network of $N = 32768$ nodes, resulting in a total of 5×10^5 walks at a given value of *p*. Independent of N, TIW can perform better than strictly adaptive walks on sparser random graphs at higher λ. The standard error is smaller than the size of the data points.

dependent upon fitness. As TIW are not explicitly driven by genotype fitness, it might happen that TIW could fail to reach a local optima. This scenario occurs when all the neighboring nodes are already traversed but none leads to a local optimum, owing to the self avoiding nature of these walks. We will discuss this particular case in further detail in the next section.

In this work, mean walk length, L_{mean}, has been studied over networks with number of genotypes (nodes), $N = 2^9, 2^{10}, 2^{11},$ and, 2^{15}. The averages were obtained for network ensembles of size $N_E = 1000$ for a given value of probability, p. A set of 1000 walks are performed on each network, resulting in a total of 10^6 walks for a given value of p, unless specified otherwise. For

$N = 2^{15}$, $N_E = 500$ resulting in total of 5×10^5 walks for a given value of p. For every network, a set of correlated fitness values governed by Equation (4) is assigned.

4. RESULTS AND DISCUSSIONS

Since TIW are not directed by fitness, questions arise as to whether TIW would be able to reach a local optimum at all. Remarkably however, we observe that *some TIW can reach a local optimum faster than even strictly adaptive walks—especially in the biologically important regime of sparseness* [50]. **Figure 2** shows the mean walk length, L_{mean}, to reach a local optimum for
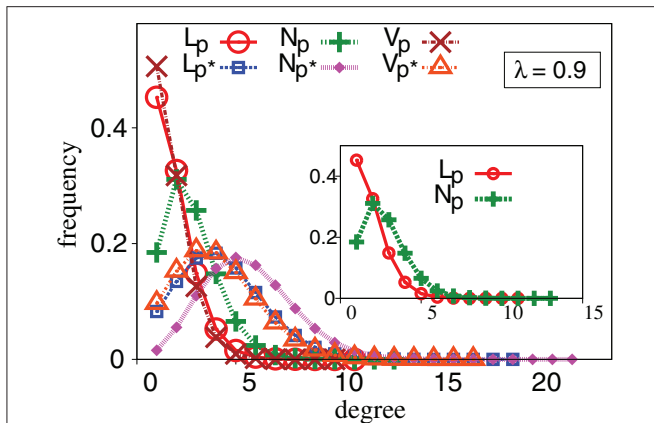
FIGURE 3 | Degree distribution profiles for different types of genotypes in a landscape: local optimum, non local optimum and valleys for $p = 0.0021$ and $p^* = 0.0053$. Observed results are for $N = 1024$, $N_E = 10^5$. The topology of the genotype space is based upon Erdös Rényi graphs. The fitness values are drawn from a bivariate Gaussian distribution with correlation parameter, $\lambda = 0.9$. All other conditions are as in **Figure 2F**.
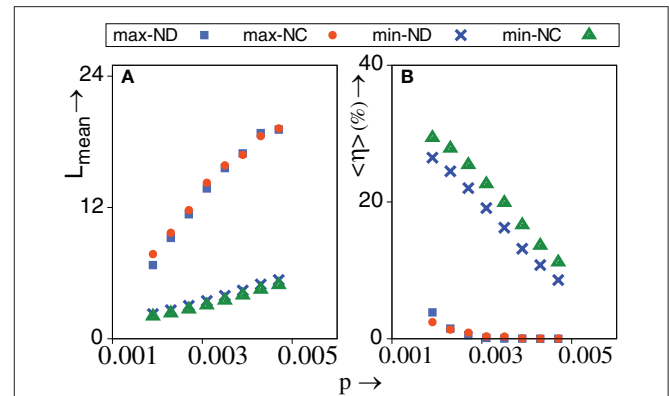

FIGURE 5 | (A) Mean walk length of various topological walks vs. p. **(B)** Percentage of ensemble averaged fraction of exhausted walks that fail to reach a local optimum vs. p. TIW are governed by minimum and maximum value of degree (ND) and closeness (NC) of nodes. $\lambda = 0.9$, $N = 1024$, $N_E = 1000$. The standard error is smaller than the size of the data points. All other conditions are as in **Figure 2F**.

FIGURE 4 | Percentage of ensemble averaged fraction of steps in a walk for which fitness decreases, $\langle n_s \rangle$, vs. p. TIW are governed by minimum and maximum value of degree (ND) and closeness (NC) of nodes. $\lambda = 0.9$, $N = 1024$, $N_E = 1000$. The standard error is smaller than the size of the data points. All other conditions are as in **Figure 2F**.
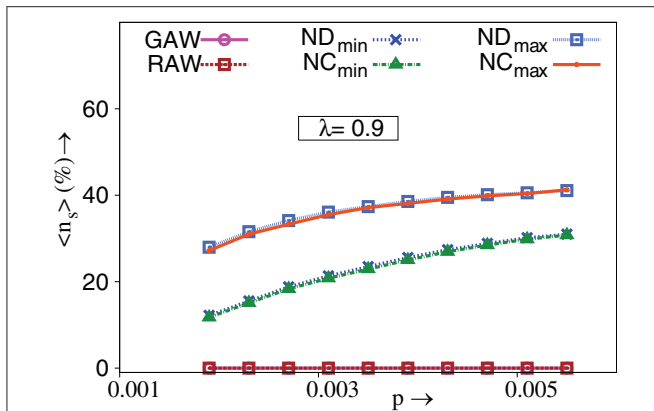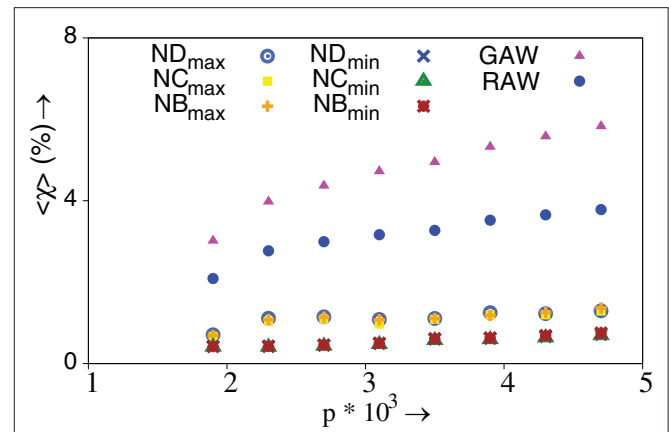

FIGURE 6 | Percentage of ensemble averaged fraction of TIW and strictly adaptive walks that reach the global optimum, χ, vs. p. TIW can be governed by the minimum and maximum value of degree (ND), closeness (NC) and betweenness (NB) of nodes. $\lambda = 0.9$, $N = 1024$, and $N_E = 40000$ with 10^5 walks performed on each network. The standard error is smaller than the size of the data points. All other conditions are as in **Figure 2F**.

different evolutionary walks, namely RAW, GAW and various TIW, with respect to probability, p in a network with $N = 512, 1024, 2048$ and 32768 genotypes. This effect gets more pronounced with increase in correlations of fitness value, λ. The basic nature of variation of L_{mean} with respect to p is similar for all values of genotypes, N, studied by us, thereby minimizing concerns about results arising as artifacts of finite size effects. The strong effect of fitness correlations over evolutionary walks on a randomly connected genotype space is well-known [4]. For completeness, degree distribution for different types of genotypes depending on their fitness profiles are shown in **Figure 3** for $\lambda = 0.9$.

As aforementioned, TIW traverse paths where neighboring nodes need not have higher fitness, unlike strictly adaptive walks. Therefore, it would be interesting to determine the extent to which TIW would permit a decrease in fitness, while venturing from one genotype to another during evolution. Let $\langle n_s \rangle$ denote the ensemble averaged fraction of steps in a walk, where there is a decrease in fitness. Obviously, $n_s = 0$ for strictly adaptive walks. As **Figure 4** shows, TIW differ significantly from strictly adaptive walks in this respect. Such action can be related to actual evolutionary processes where to reach a local peak of the fitness landscape, the population may choose a less fitter mutation for their eventual survival in the long run [30, 31]. Thus TIW, exhibit the characteristic of passing through genotypes with lower fitness, and can successfully model non-adaptive evolutionary experiments as discussed in the earlier section. As mentioned therein, *in vitro* evolutionary experiments with *E. coli* [30], *S. typhimurium* [31] and *in vivo* experiments with

TEM-1 β-lactamase [9, 24] display this effect. These results on TIW are also in agreement with the evolutionary study on lac operon where evolutionary paths connecting 19 fitness peaks in the experimental fitness landscape, pass through valleys [29].

Notably, **Figure 5A** shows that the mean walk length of max-directed TIW is much larger than min-directed TIW. While strictly adaptive walks are guaranteed to reach a local optimum, TIW may not reach a local optimum but might remain at a non local optimum. The propensity to remain in a non local optimum indicates the inability of the genotype to evolve any further. Such situations could correspond to unavailability of fitter mutants or significant selection pressure cast upon the genetic state of a population due to change in environmental variables. Hence, such walks can be associated with routes toward extinction when a population fails to adapt [55–57]. Let W_T^r denote the total number of walks on the rth network ensemble until a specified number of "successful" walks, W_S^r, can be achieved. Obviously, here a "successful" walk refers to one where a local optimum is reached. Herein, we choose $W_S^r = 1000, \forall r$. A number of walks, W_E^r are "exhausted" toward achieving W_S^r walks, because these walks do not end up at a local optimum. The ensemble averaged fraction of such exhausted walks is, $\langle \eta \rangle = \langle W_E/W_T \rangle$. Obviously, $\eta = 0$ for strictly adaptive walks. Interestingly, **Figure 5B** shows that max-directed TIW are far more successful than min-directed TIW in reaching a local optimum.

We further compare the fraction of TIW which successfully reach the *global optimum*. Let, W_G^r be the number of walks that reach the global optimum for the *rth* network ensemble. Then, the ensemble averaged fraction of such walks is, $\langle \chi \rangle = \langle W_G/W_T \rangle$, where W_T is defined earlier in the text. We find that max-directed TIW outperform min-directed TIW as shown in **Figure 6**. However, we also note that RAW and GAW has a higher chance to reach the global optimum—which is not surprising. We wish to emphasize that there neither of max-TIW or min TIW is consistently better or preferred. Indeed, we encounter an interesting tradeoff when it comes to choosing the "better" TIW. On one hand, max-directed TIW possess a higher chance of reaching the global optimum and are more "successful" in reaching a local optimum. On the other hand, min-directed TIW have a far smaller mean walk length for reaching a local optimum.

Our results are in broad agreement with known evolutionary facts. In a fitness landscape, the degree of a genotype indicates the availability of viable mutations. A high degree genotype enjoys the luxury of a broad range of viable mutations. This seems to be associated with phenotypic diversity [58]. For example, the vast majority of *lin* mutations are viable while few are not [59]. On the other hand, a low degree genotype in a fitness landscape has access to a lesser number of viable mutations. It should be especially noted that availability of lesser options for viable mutations does not mean that such genes are unimportant in any way. In fact, the chances of

viable mutations for *essential genes* are extremely low, as well known. Thus, evolution is likely to choose rather conserved paths having such low degree nodes [60]. However, at the same time, such paths may fail to reach a local optimum due to limitations in genetic variation. Evolution may also prefer genotypes with a higher degree, as in maximum-degree directed TIW, to increase the phenotypic possibilities in adverse conditions. Maximum-degree directed walks can therefore explore larger part of the landscape due to constant availability of a higher number of viable options. Thus they have a higher probability in reaching a local optimum as compared to minimum-degree directed walks, which is reflected in **Figure 5B**.

5. CONCLUSION

In summary, modeling evolutionary walks on randomly connected fitness landscapes by using topology rather than fitness sheds new insight into evolutionary patterns. We introduce the notion of topologically inspired walks. These walks are dictated by the topology of connections in the fitness landscape and are not dependent on fitness. TIW are not always hill climbing and can go through hills and valleys as seen in experiments [9, 24, 30, 31, 49, 61]. We have also considered isolated genotypes due to the presence of lethal mutants [4, 5, 37] in our model of correlated [26, 27] fitness landscapes. Interesting tradeoffs are observed between topological walks directed by the minimum and maximum value of any given network metric. The mean length of adaptive walks, L_{mean} does not exhibit a remarkable qualitative and indeed quantitative dependence upon the topology of the underlying fitness landscape [4]. L_{mean} is slightly smaller for networks with a scale-free degree distribution (SF) when compared to ER networks on correlated fitness landscapes [4]. This could be due to the reason that in SF networks—the shortest path length, l, between two randomly chosen nodes on a network of N nodes exhibits $l \propto log\, log\, N$ [62, 63]. On the other hand, in ER networks $l \propto logN$ [64]. Nevertheless, it would be interesting to see how TIW perform on scale free networks or even on random networks with connection probabilities dependent on fitness. Also, it would be interesting to compare how TIW fare vis-a-vis fitness biased random walks or foraging random walks which have been studied well in literature [65–67].

AUTHOR CONTRIBUTIONS

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