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Evolutionary escape from local fitness peaks through inversion mutations

Leonardo Trujillo, Paul Banse & Guillaume Beslon

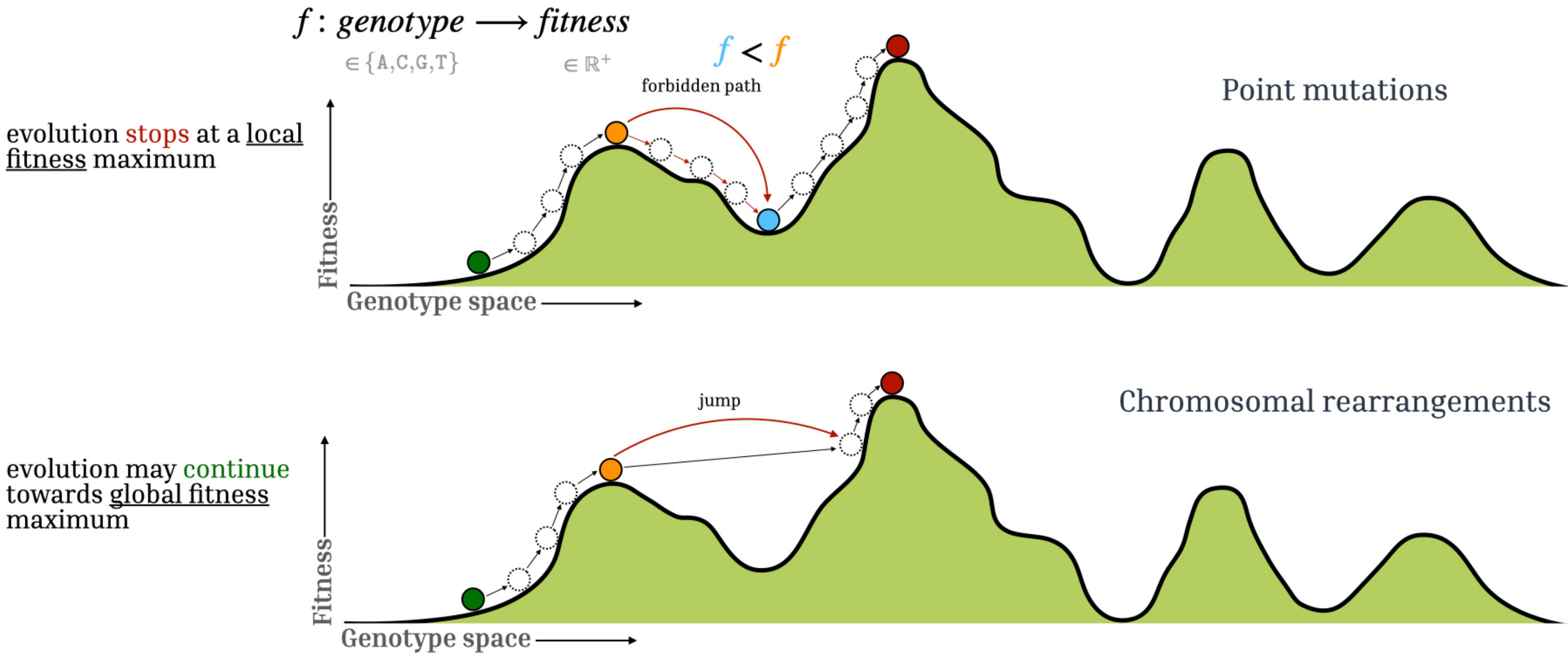
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Model of molecular evolution

Adaptive molecular evolution is often conceptualised as **adaptive walks on rugged fitness landscapes** that are driven by changes in the genome (mutations).

The problem

Once a local fitness peak is reached there are no more selectively accessible pathways by the mechanism of single nucleotides (point) mutations. Then, the evolutionary dynamics get stuck in a suboptimal peak, hindering any possibility to reach other higher peaks.



Proposition

We introduce a simple computational model to simulate the escaping process from a local fitness peak combining point and inversion mutations.

Algorithm 1: Mutate (x, i, j, N)

```
input:  $x \in \{0, 1\}^N, [i, j] \in \{1, \dots, N\}$ 
1:  $l \leftarrow i$ 
2: repeat
3:    $x_{temp} \leftarrow (1 - x_i)$ 
4:    $x_i \leftarrow (1 - x_j)$ 
5:    $x_j \leftarrow x_{temp}$ 
6:    $i \leftarrow i + 1 \bmod N$ 
7:    $j \leftarrow j - 1 \bmod N$ 
8: until  $j = l$ 
9:  $y \leftarrow x$ 
10: return  $y \in \{0, 1\}^N$ 
```

Algorithm 2: AdaptiveWalk (x, p, N, τ_{max})

```
input:  $x \in \{0, 1\}^N, \tau_{max}, p \in (0, 1)$ 
1:  $t \leftarrow 0$ 
2:  $f_0 \leftarrow f(x)$ 
3: repeat
4:   if  $p = 1$  then
5:      $i, j \leftarrow \text{PRNG}$ 
6:   else
7:      $i \leftarrow \text{PRNG}$ 
8:      $j = i$ 
9:   end if
10:   $y \leftarrow \text{Mutate}(x, i, j, N)$ 
11:   $f' \leftarrow f(y)$ 
12:  if  $f_t < f'$  then
13:     $x \leftarrow y$ 
14:     $f_{t+1} \leftarrow f'$ 
15:  else
16:     $f_{t+1} \leftarrow f_t$ 
17:  end if
18:   $t \leftarrow t + 1$ 
19: until  $t = \tau_{max}$ 
output:  $y \in \{0, 1\}^N, f(y) \in [0, 1]$ 
```

Inversion mutations operation

5' - ATCGATTGAGCTTAGCG - 3' $\xrightarrow{\{A,C,G,T\} \rightarrow \{0,1\}}$ 011001100011110010
3' - TACGATTCAGCTTAGCG - 5' 100110011100001101

Inspired by molecular biology, these genotypes are **double-strained** binary vectors of length N

$$x := (x_1, x_2, \dots, x_N, \dots, x_N), \quad x_i \in \{0, 1\}$$

where the **complementary** vector is defined such that $\bar{x}_i = 1 - x_i$

$$\begin{matrix} 011 & 0 & 011000111 & 1 & 0010 \\ 100 & 1 & 100111000 & 0 & 1101 \end{matrix} \longrightarrow \begin{matrix} 011 & 0 & 000111001 & 1 & 0010 \\ 100 & 1 & 111000110 & 0 & 1101 \end{matrix}$$

We model the **chromosomal-like inversion** as a two step procedure:

$$\hat{I} = \hat{C} \circ \hat{P}$$

1. **Conjugation operation**
 $\hat{C}: (x_p, x_{p+1}, \dots, x_{j-1}, x_j) \longrightarrow (\bar{x}_p, \bar{x}_{p+1}, \dots, \bar{x}_{j-1}, \bar{x}_j)$

2. **Permutation operation**
 $\hat{P}: (x_p, x_{p+1}, \dots, x_{j-1}, x_j) \longrightarrow (x_p, x_{j-1}, \dots, x_{p+1}, x_j)$

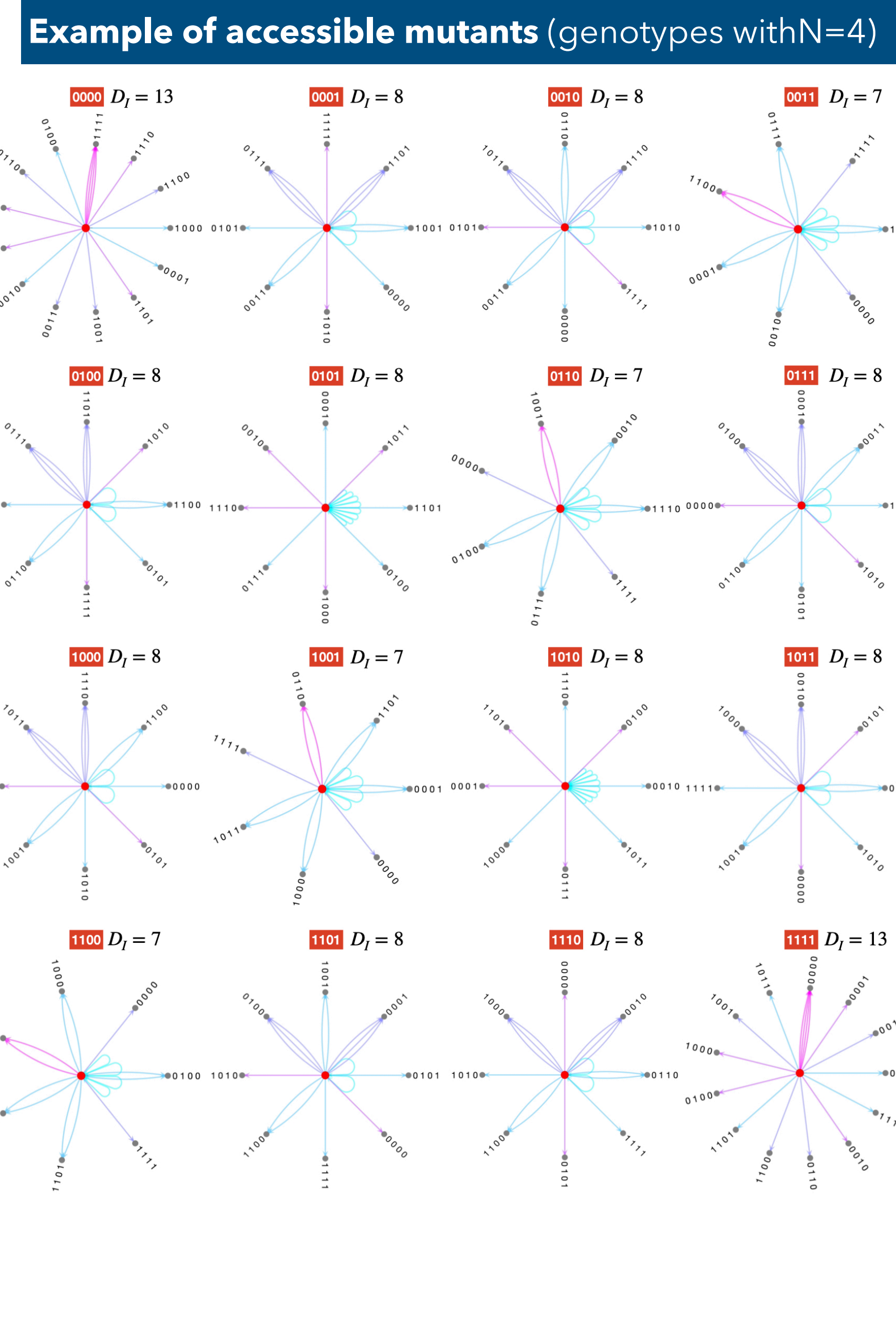
(point-mutations when: $i=j$)

$$\begin{matrix} 011001110 & 0 & 011110010 & 1 & 011110010 \\ 100110011 & 1 & 100001101 & 0 & 100001101 \end{matrix} \xrightarrow{\text{switch}} \begin{matrix} 011001110 & 1 & 011110010 \\ 100110011 & 0 & 100001101 \end{matrix}$$

Enumeration of accessible mutants

Examples of the number of neighbouring sequences D per genotype of size N (subscripts numbers are the occurrence frequencies of D).

N	D_I	D_P
2	$2_2, 3_2$	2
3	$5_6, 7_2$	3
4	$7_4, 8_{10}, 13_2$	4
5	$13_{20}, 17_{10}, 21_2$	5
6	$16_{30}, 17_{18}, 18_2, 22_{12}, 31_2$	6
7	$25_{70}, 29_{42}, 37_{14}, 43_2$	7
8	$28_{16}, 29_{52}, 30_{112}, 32_2, 34_8, 36_{48}, 46_{16}, 57_2$	8
9	$39_6, 40_{18}, 41_{234}, 45_{162}, 52_{36}, 53_{36}, 64_{18}, 73_2$	9
10	$45_{100}, 46_{150}, 47_{420}, 50_2, 52_{40}, 53_{200}, 62_{40}, 63_{50}, 77_{20}, 91_2$	10



Accessible-mutants graphs

Representative examples for $N = 4, 7$ and 10 . Colours indicates the nodes degree. The reported values correspond to the mean degree $\langle k \rangle$ and the maximum degree Δ . The upper graphs show the point mutation case, verifying that the accessible-mutants graphs are isomorphic to the Hamming graphs $H(4, 2)$; $(7, 2)$ and $H(10, 2)$, i.e. the hypercubes $Q(N)$ (the genotype space). The lower graphs correspond to the inversion mutations cases, where we can appreciate that the accessible-mutants graphs are not isomorphic to their respective genotype (hypercubic) spaces.

NK rugged landscape

As a model for rugged fitness landscapes, we adopt the well known Kauffman NK model (N is the length of the genome and K is the "epistatic" coupling between nucleotides)

The fitness per bit
 $f_i: \{0, 1\}^{K+1} \rightarrow [0, 1]$

Example:
 $N = 16$
 $K = 2$

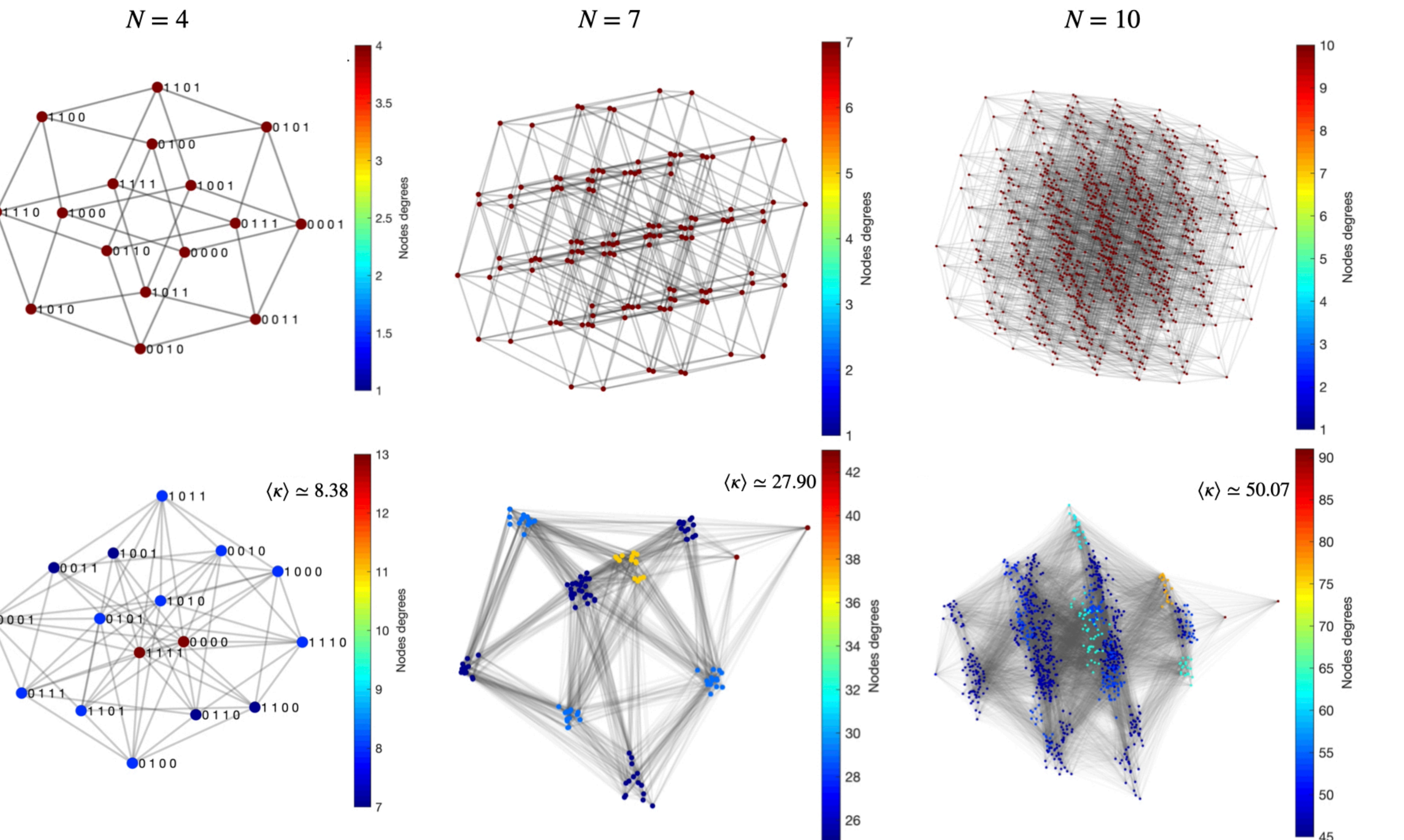
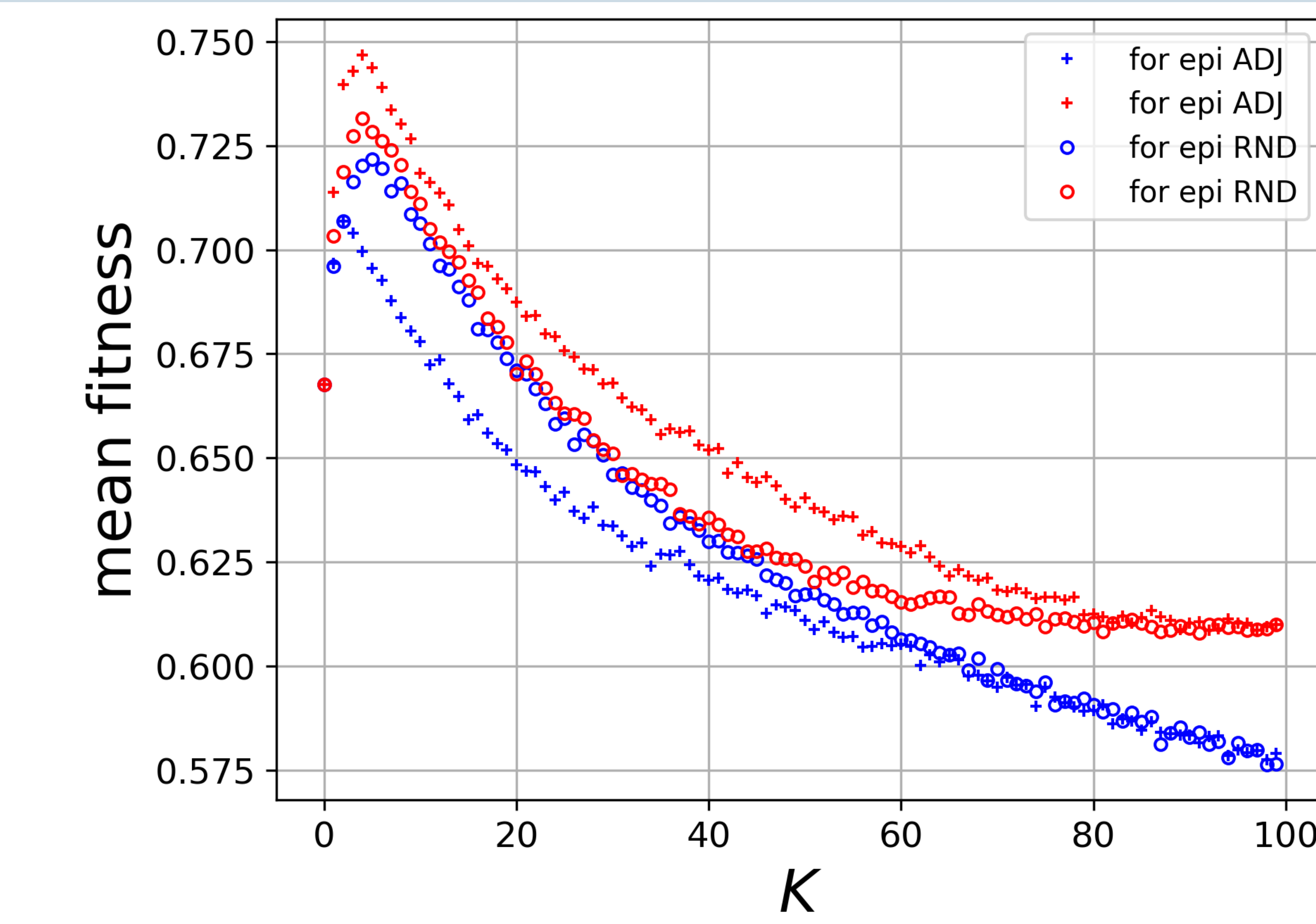
The total fitness
$$f = \frac{1}{N} \sum_{i=1}^N f_i(x_1, x_2, \dots, x_N)$$

Adaptive walks

We assume that on a population scale the organisms are isogenic (i.e. population only contains copies of one genotype) and, therefore, can be simulated as the evolution of one genotype. We consider the simplest case of random adaptive walks, where available genomes with higher fitness are chosen at random. So, the biological significance of our model must be framed in the of strong selection weak mutations limit.

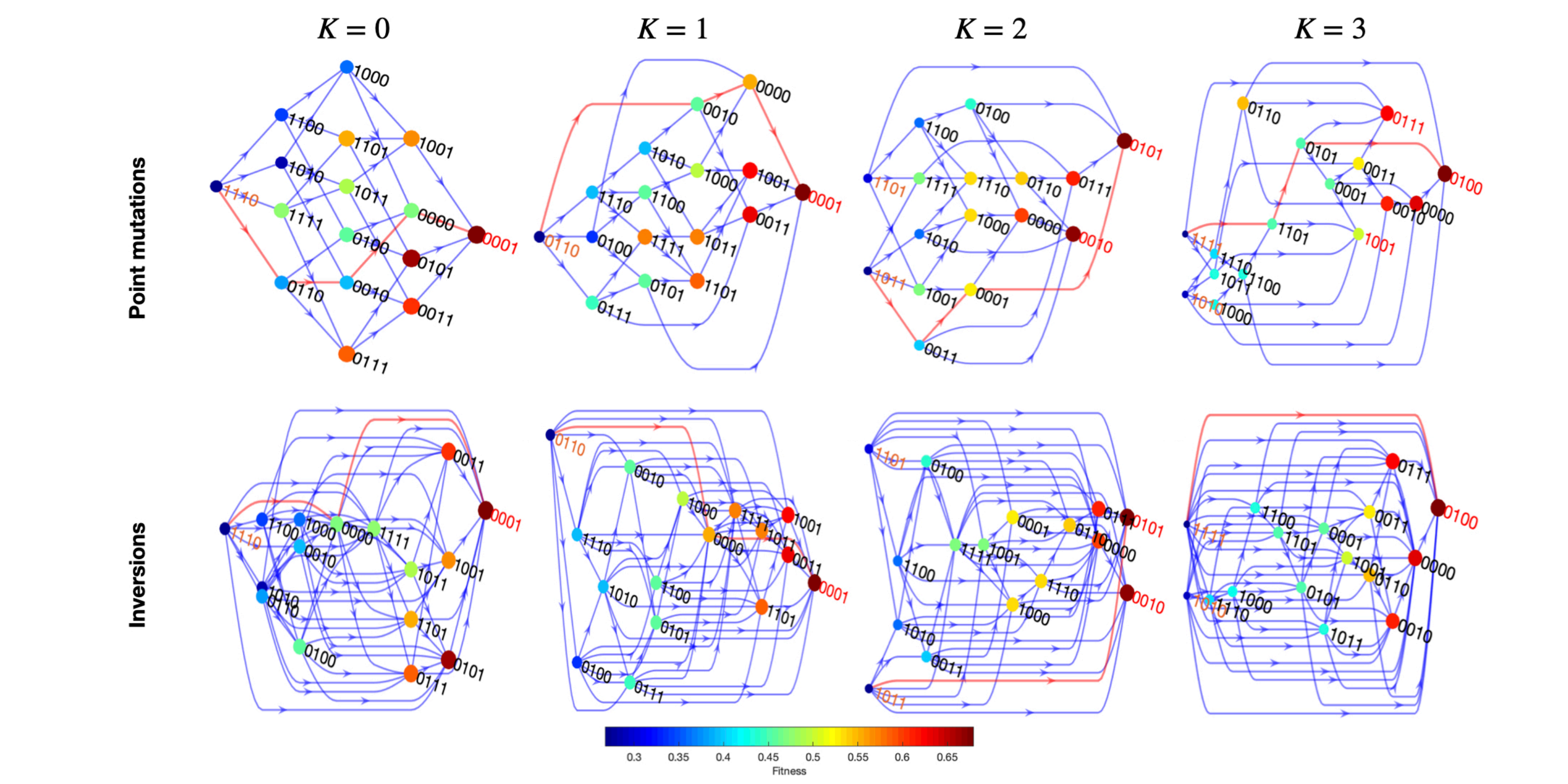
Fitness and epistatic interaction

Behaviour of the mean fitness of genotypes with size $N=100$ for different rugged landscapes, tuned through $K=0, \dots, 99$. For adjacent (+) and random (o) neighbourhoods interactions. Red color corresponds to inversion mutations and blue to point mutations.



NK fitness networks

Representatives instances of the NK model for $N = 4$ and their fitness networks in layered representation. Node colours correspond to fitness values, increasing from left to right. The shortest paths from lowest to highest fitness genotypes are highlighted in red. The top row shows the cases for point mutations, while the bottom row corresponds to inversion mutations. The landscapes ruggedness go from single peaks $K = 0$, intermediate ruggedness $K = 1, K = 2$, and the full rugged case $K = 3$.



Summary

This work provided computational evidence that once an adaptive walk reaches a local fitness peak, then inversion mutations can redirect the evolutionary process towards genotypes with higher fitness values. The way our model was conceived, also proves that escape from a local peak of fitness can occur in constant environments without contingencies. Our model for inversion mutations not only elucidated an escape mechanism, but have also made it possible to uncover interesting aspects about the combinatorics of inversion mutations. We have been able to contrast the isomorphism of mutational graphs for point mutations and their isomorphism with the genotype space. Finally, it was possible to verify that for a very simple model of population genetics in the strong weak mutation selection limit –with rugged landscapes simulated with the well know NK model– our adaptive walks simulations showed that when the evolutionary dynamics is driven by inversions, higher fitness values can be reached.

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