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Evolutionary escape from local fitness peaks through inversion mutations

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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.

$$f: \text{genotype} \rightarrow \text{fitness}$$

$$\in \{A, C, G, T\} \in \mathbb{R}^+$$

$$f < f'$$

forbidden path

Point mutations

Chromosomal rearrangements

evolution stops at a local fitness maximum

evolution may continue towards global fitness maximum

Genotype space

Genotype space

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 ∈ {0, 1}^N, [i, j] ∈ {1, ..., N}
1: l ← i
2: repeat
3:   x_temp ← (1 - x_i)
4:   x_i ← (1 - x_j)
5:   x_j ← x_temp
6:   i ← i + 1 mod N
7:   j ← j - 1 mod N
8: until j = l
9: y ← x
10: return y ∈ {0, 1}^N
    
```

Algorithm 2: AdaptiveWalk (x, p, N, τ_max)

```

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

Inversion mutations operation

5' - ATCGATTGAGCTCTAGCC - 3' (A,C,G,T) → {0,1} 011001100011110010
 3' - ATGCLVYVLOLVQVYVLDCC - 5' 100110011100001101

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

$$x := (x_1, x_2, \dots, x_N, \dots, x_N, \dots, x_1)$$

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

$$01100110001110010 \rightarrow 011000011100110010$$

$$100110011100001101 \rightarrow 100111100011011101$$

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

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

1. Conjugation operation

$$\hat{C}: (x_1, x_2, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_{j-1}, x_j, x_{j+1}, \dots, x_N) \rightarrow (\bar{x}_1, \bar{x}_2, \dots, \bar{x}_{i-1}, \bar{x}_i, \dots, \bar{x}_{j-1}, \bar{x}_j, \dots, \bar{x}_N)$$

2. Permutation operation:

$$\hat{P}: (x_1, x_2, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_{j-1}, x_j, x_{j+1}, \dots, x_N) \rightarrow (x_j, x_{j+1}, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_N)$$

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

$$01100110001110010 \xrightarrow{\text{switch}} 011001100110010$$

$$100110011100001101 \xrightarrow{\text{switch}} 10011001100001101$$

The model

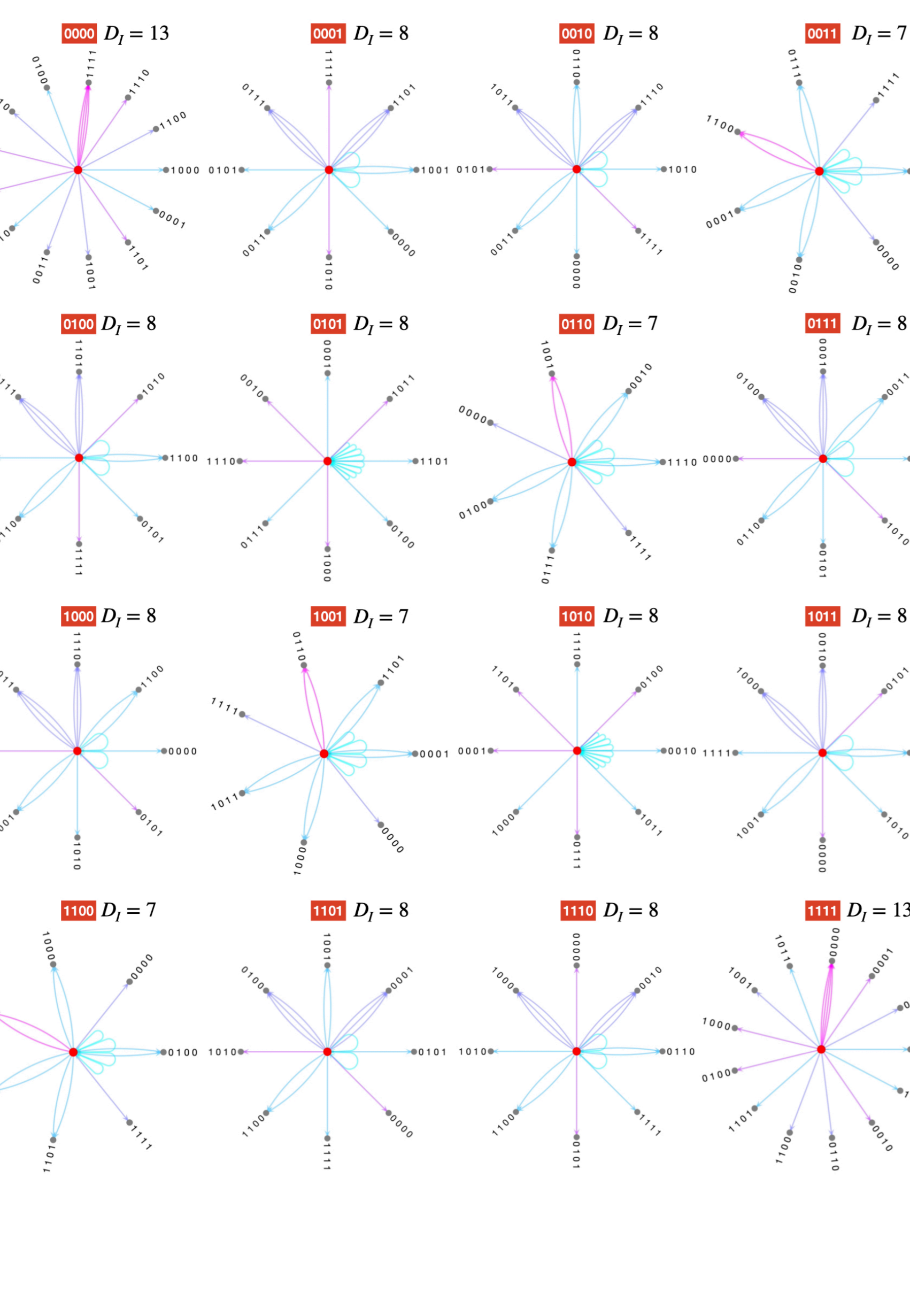
We simulate artificial molecular evolution of digital organisms (replicators), each of which contains a single piece of DNA. We engineer a computational method to cartoon the double-stranded structure of DNA, and simulate inversion-like mutations: a permutation of the complementary strand, which are then exchanged with the main strand within the segment where the inversion occurs. We model digital genotypes made up of a binary alphabet {0, 1}. In analogy with DNA primary sequence, the bits represent (artificial binary) nucleotides. We also assume that genomes are arranged in circular strings with constant number of base-pairs. In an abstract sense, our model does not consider non-coding regions, mimicking the molecular evolution of some viruses and mitochondrial DNA with compact genomes and closed double-stranded DNA circles. It is important to emphasise that our computational model simulates intragenic-like mutations. We do not include recombination, so we are modelling asexual replication.

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).

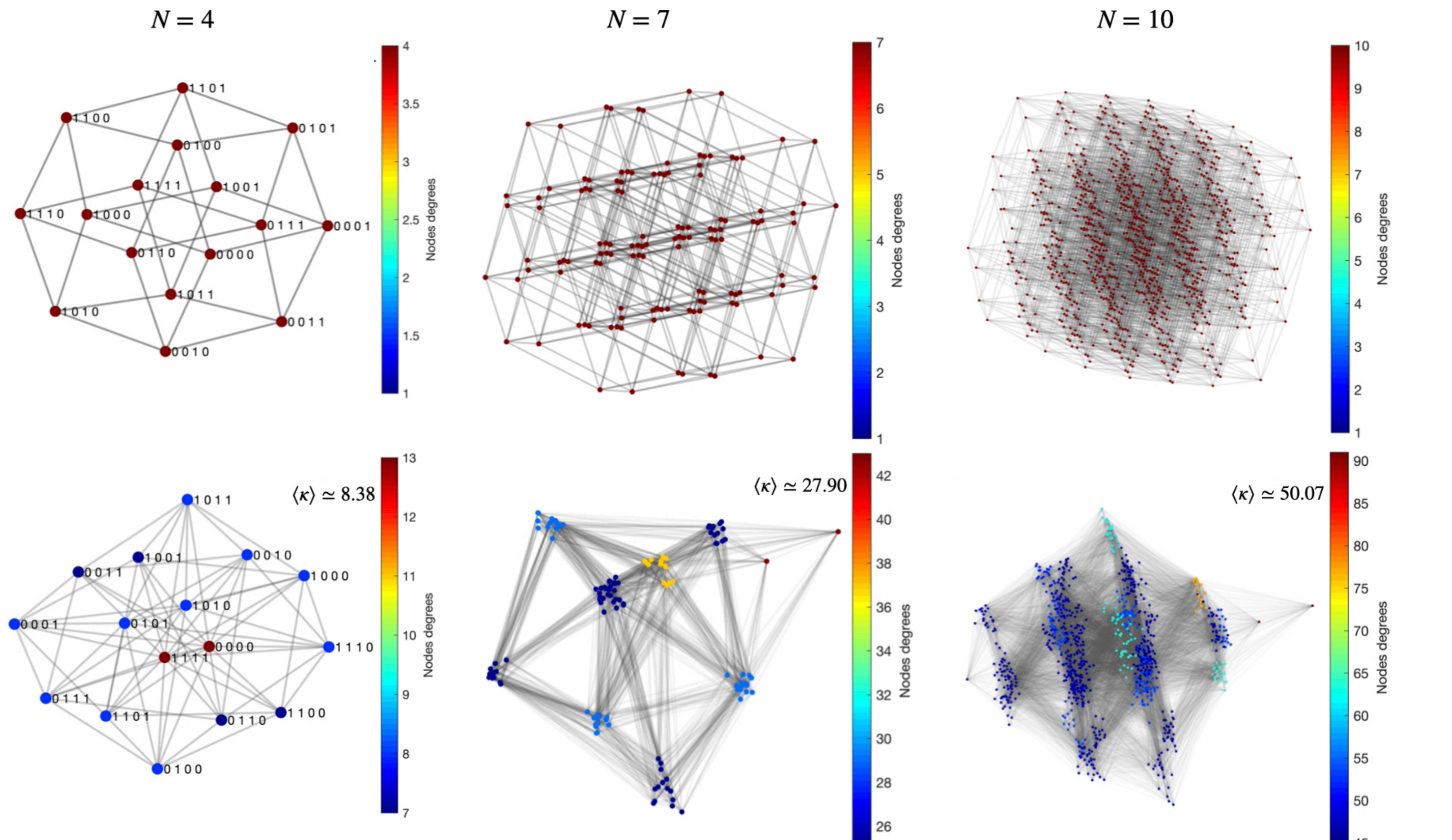
N	D _i	D _P
2	2 ₂ , 3 ₂	2
3	5 ₆ , 7 ₂	3
4	7 ₄ , 8 ₁₀ , 13 ₂	4
5	13 ₂₀ , 17 ₁₀ , 21 ₂	5
6	16 ₃₀ , 17 ₁₈ , 18 ₂ , 22 ₁₂ , 31 ₂	6
7	25 ₇₀ , 29 ₄₂ , 37 ₁₄ , 43 ₂	7
8	28 ₁₆ , 29 ₃₂ , 30 ₁₂ , 32 ₂ , 34 ₈ , 36 ₄₈ , 46 ₁₆ , 57 ₂	8
9	39 ₆ , 40 ₁₈ , 41 ₂₄ , 45 ₁₆₂ , 52 ₃₆ , 53 ₃₆ , 64 ₁₈ , 73 ₂	9
10	45 ₁₀₀ , 46 ₁₅₀ , 47 ₂₀ , 50 ₂ , 52 ₄₀ , 53 ₂₀₀ , 62 ₄₀ , 63 ₅₀ , 77 ₂₀ , 91 ₂	10

Example of accessible mutants (genotypes with N=4)



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 k_{max} . 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 (hypercube) 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)

$$f_i: \{0,1\}^{K+1} \rightarrow [0,1]$$

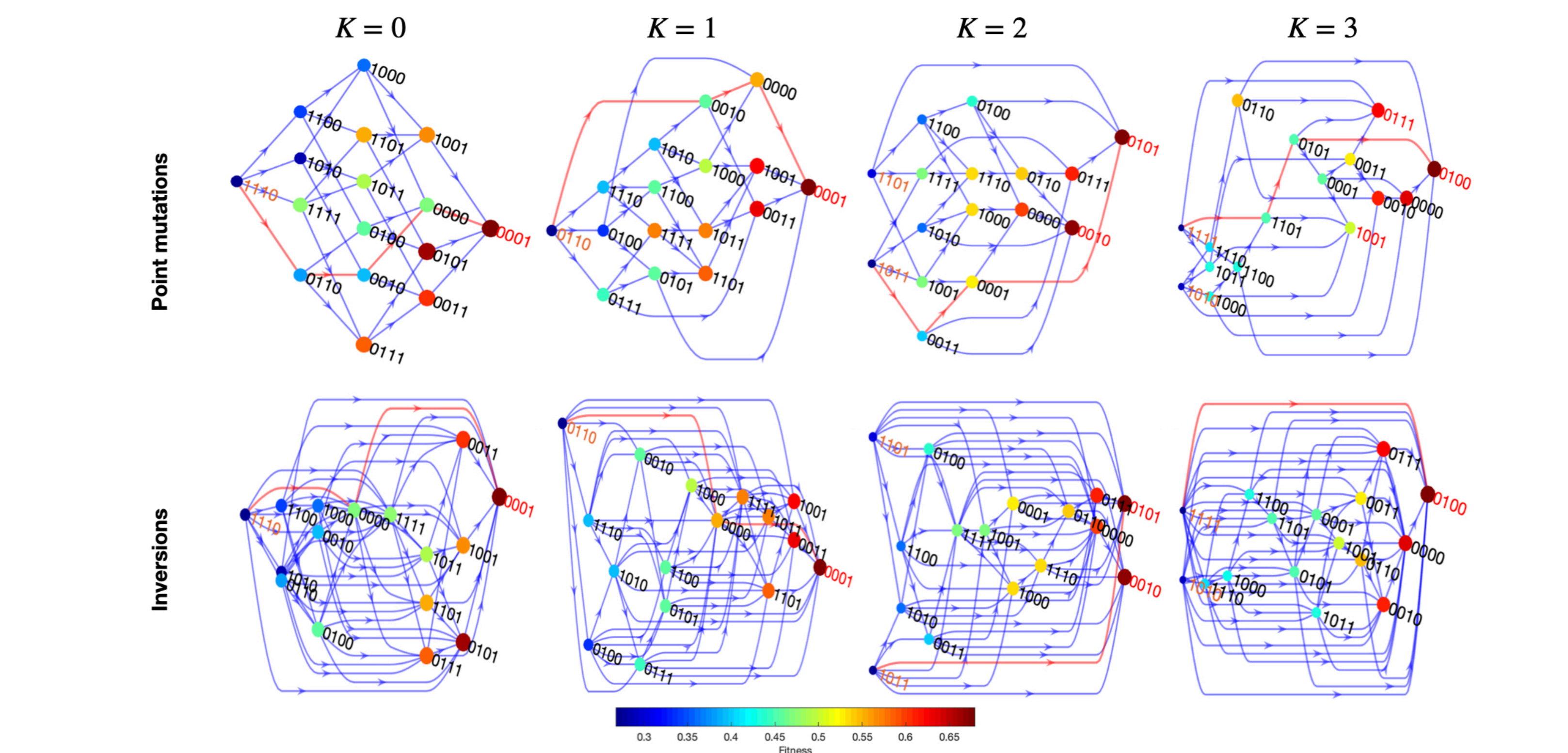
$$f = \frac{1}{N} \sum_{i=1}^N f_i(x_1, x_2, \dots, x_{K+1})$$

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.

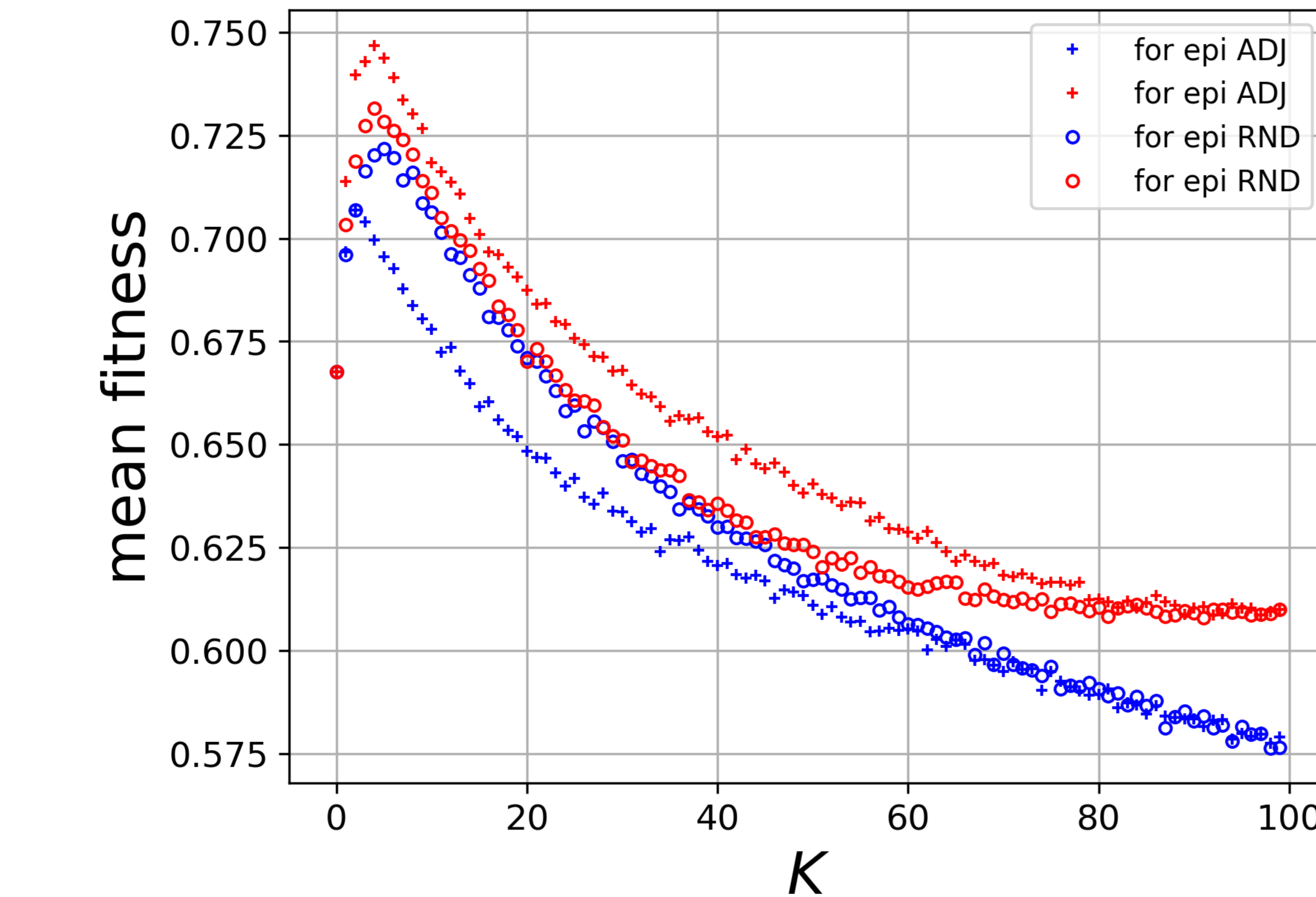
NK fitness networks

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 $K = 3$.



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.



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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