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Testing evolution predictability using the aevol software

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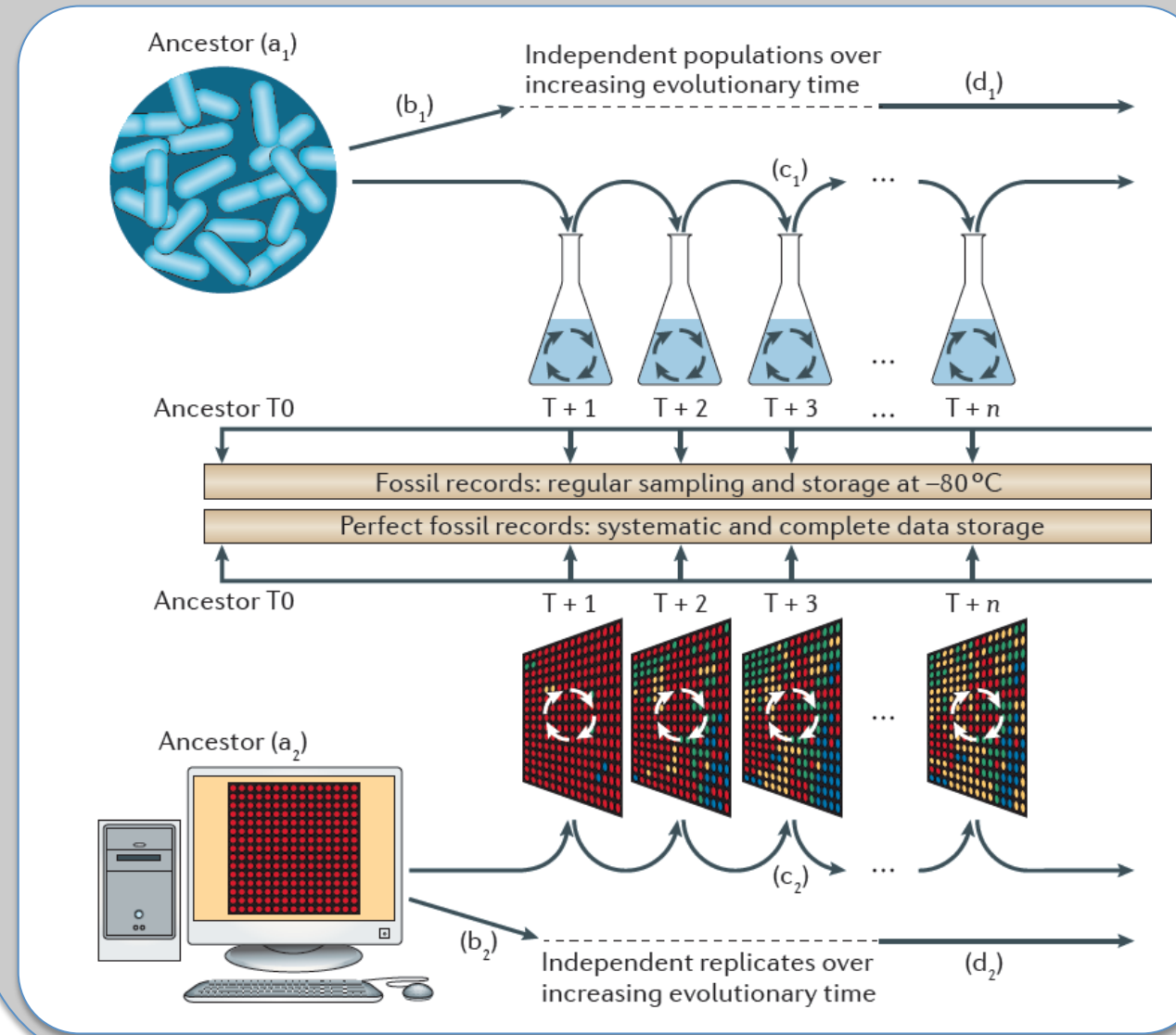
2: IBMCP (CSIC-UPV), Valencia, Spain; 3: Santa Fe Institute, Santa Fe NM, USA

Abstract

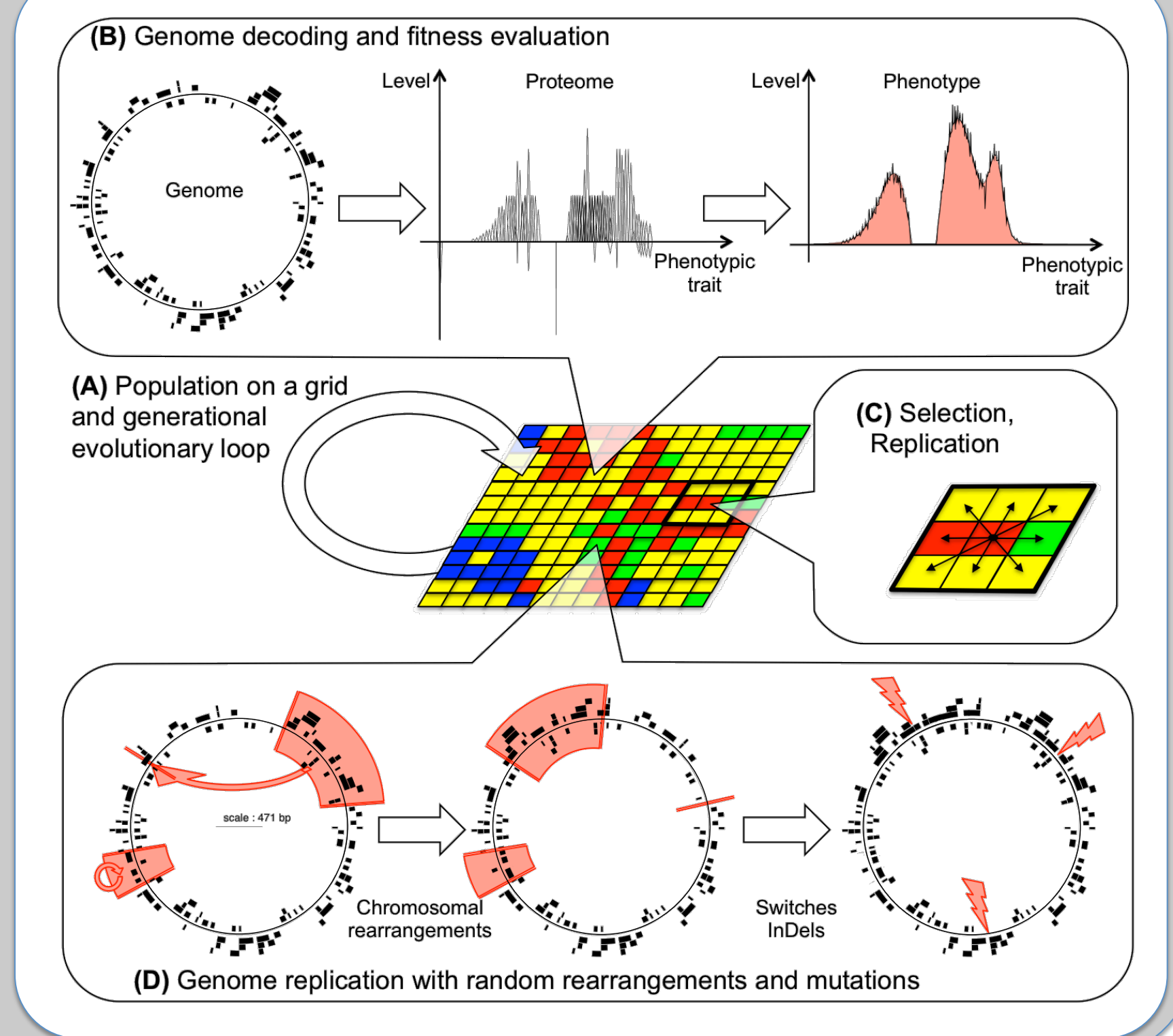
Motivated by RNA virus' genome biology, we used the aevol software to simulate the evolution of compacted genomes under high mutation rates. 30 independent digital wild-type (WT) genomes were generated after 200,000 generations of evolution under similar conditions. Then, each of these WTs was cloned 30 times and we let evolution to continue for 30,000 extra generations. By comparing these clones, we aimed to reveal the extent of evolutionary predictability for such compacted genomes. Results show that: (i) WTs are not equivalent in terms of evolutionary potential: some WTs are more prone than the others to increase their fitness during the last 30,000 generations. (ii) Evolution frequently occurs in bursts which implies that the probability to fix a mutation is increased after fixation of another mutation. Moreover these bursts are often initiated by chromosomal rearrangements (mainly duplications) because these rearrangements open new evolutionary pathways in the fitness landscape. Indeed, we quantified the "evolvability potential" of every clone after each mutation and found that the bursts are triggered by a strong increase of evolvability that quickly leads to point substitutions and indels fixation.

Methods: *in silico* experimental evolution (ISEE) with the aevol platform

Aevol (www.aevol.fr) is an *ISEE* platform that models bacteria at the genomic level with explicit mutation and selection processes. *ISEE* mimics experimental evolution with *in silico* organisms subjected to variation and selection in a computer.



- (A) Population simulated on a grid.
- (B) Realistic genome model. Abstract phenotypic task (target matching).
- (C) Local competition and replication on the grid.
- (D) Mutational process including local events (point substitutions and indels) and large chromosomal rearrangements



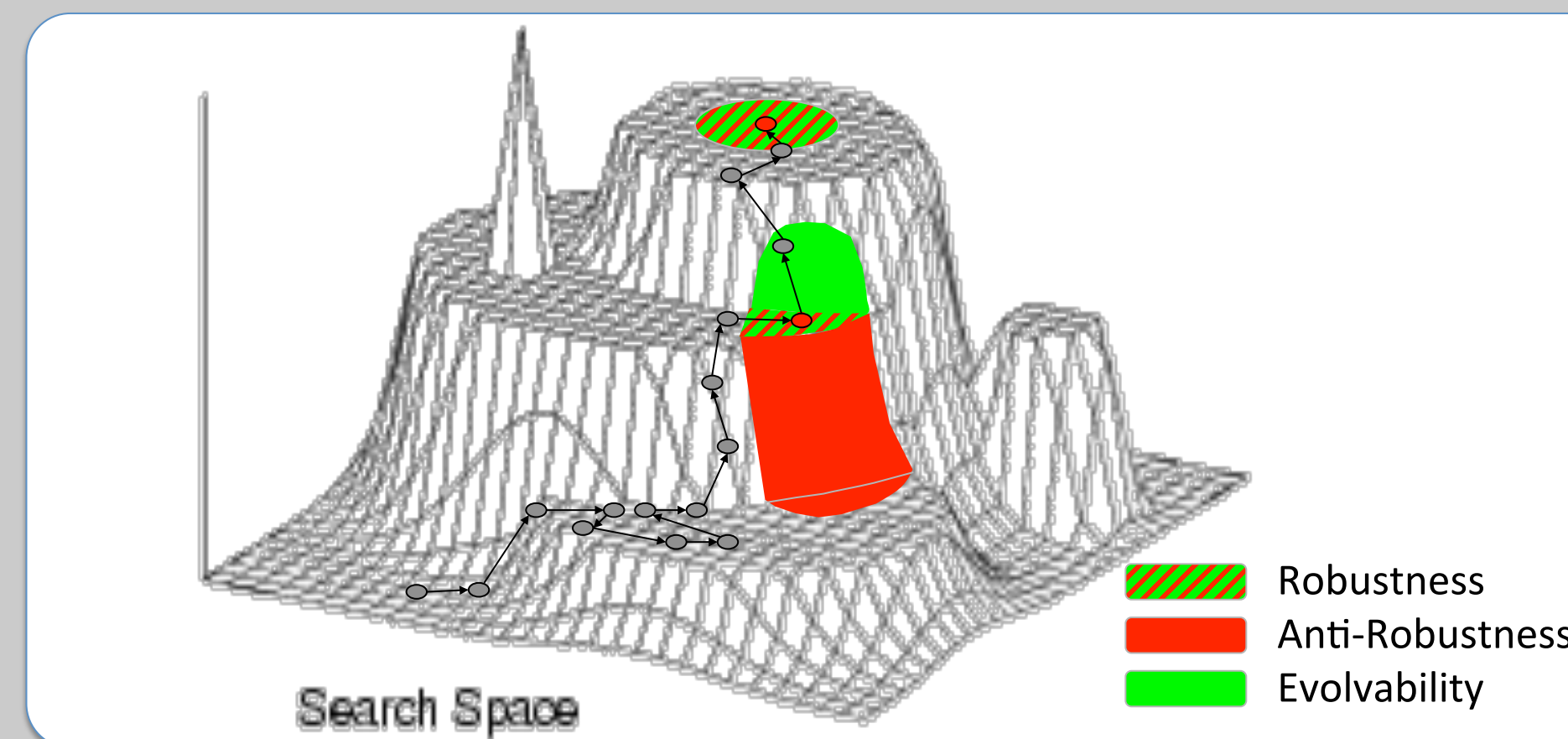
Experimental design

Strain generation:

- 30 WT virus-like genomes have been generated by evolving populations of 4096 individuals up to 200,000 generations under high mutational pressure (10^{-4} mutations/site/generation).
- Each WT strain has been cloned 30 times, and evolved for 30,000 further generations.
- The 900 lineages have then been scrutinized to study the dynamics of innovation and seek for evolutionary predictability by analyzing:
 - The evolution of fitness during 25,000 generations.
 - The evolutionary trajectories (fixed mutations).
 - The local curvature of the fitness landscape along the evolutionary trajectory.

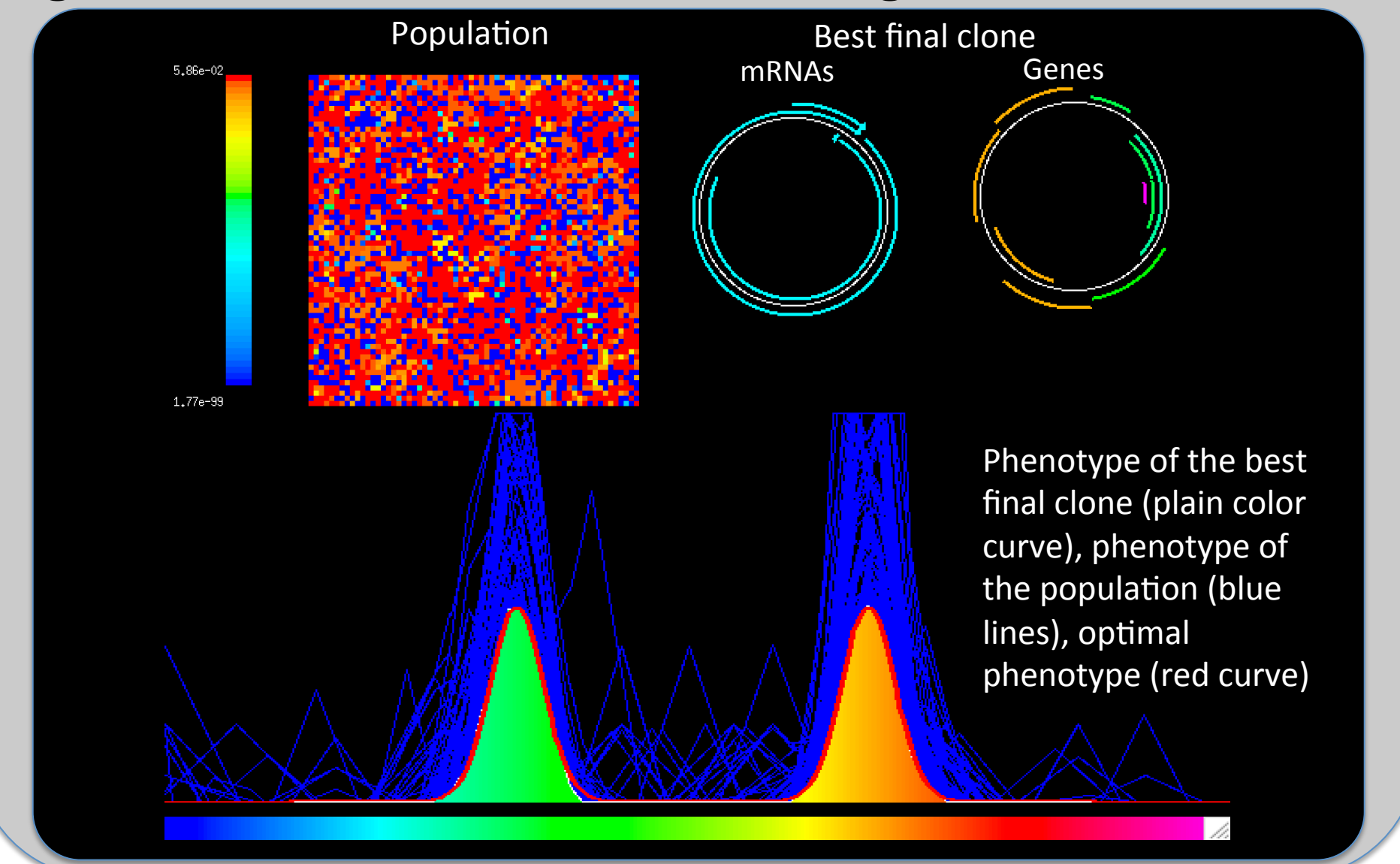
Local sampling of the fitness landscape:

- For each ancestral genotype of the 900 lineages we generated 10,000,000 offspring.
- From these offspring we can estimate the evolution of robustness, anti-robustness and evolvability along the evolutionary path.



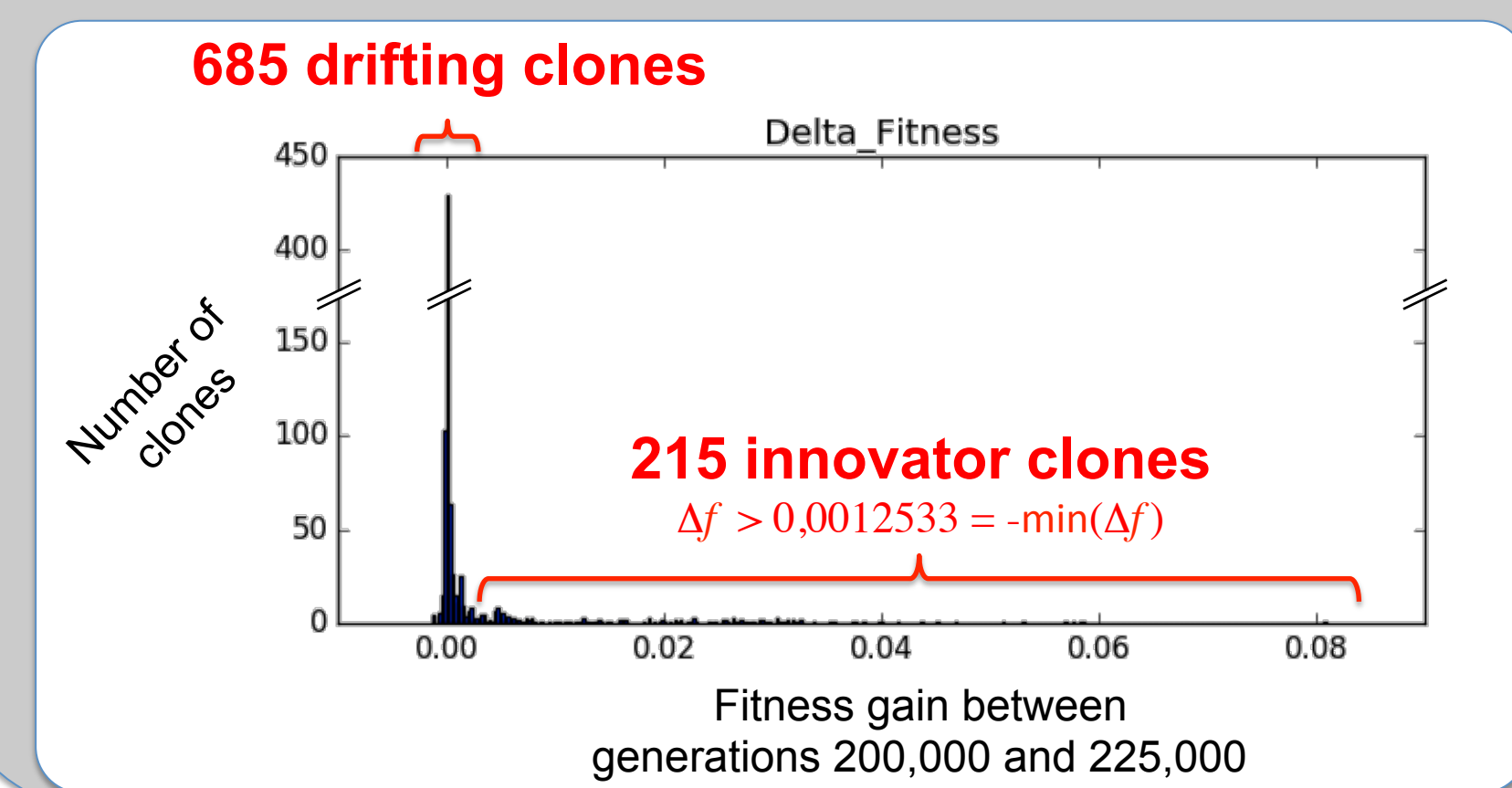
Results (1): Virus-like genomes

The high mutation rates lead to the evolution of virus-like organisms: small genomes, around 10 coding sequences, few mRNAs, overlapping genes, and almost no non-coding base.



Drift vs innovation in the 900 clones:

- 163 clones have lost fitness between generations 200,000 and 225,000.
- 251 kept their ancestral fitness.
- 271 marginally improved their fitness.
- 215 significantly improved fitness; 50% of these "innovators" come from 7 WTs.



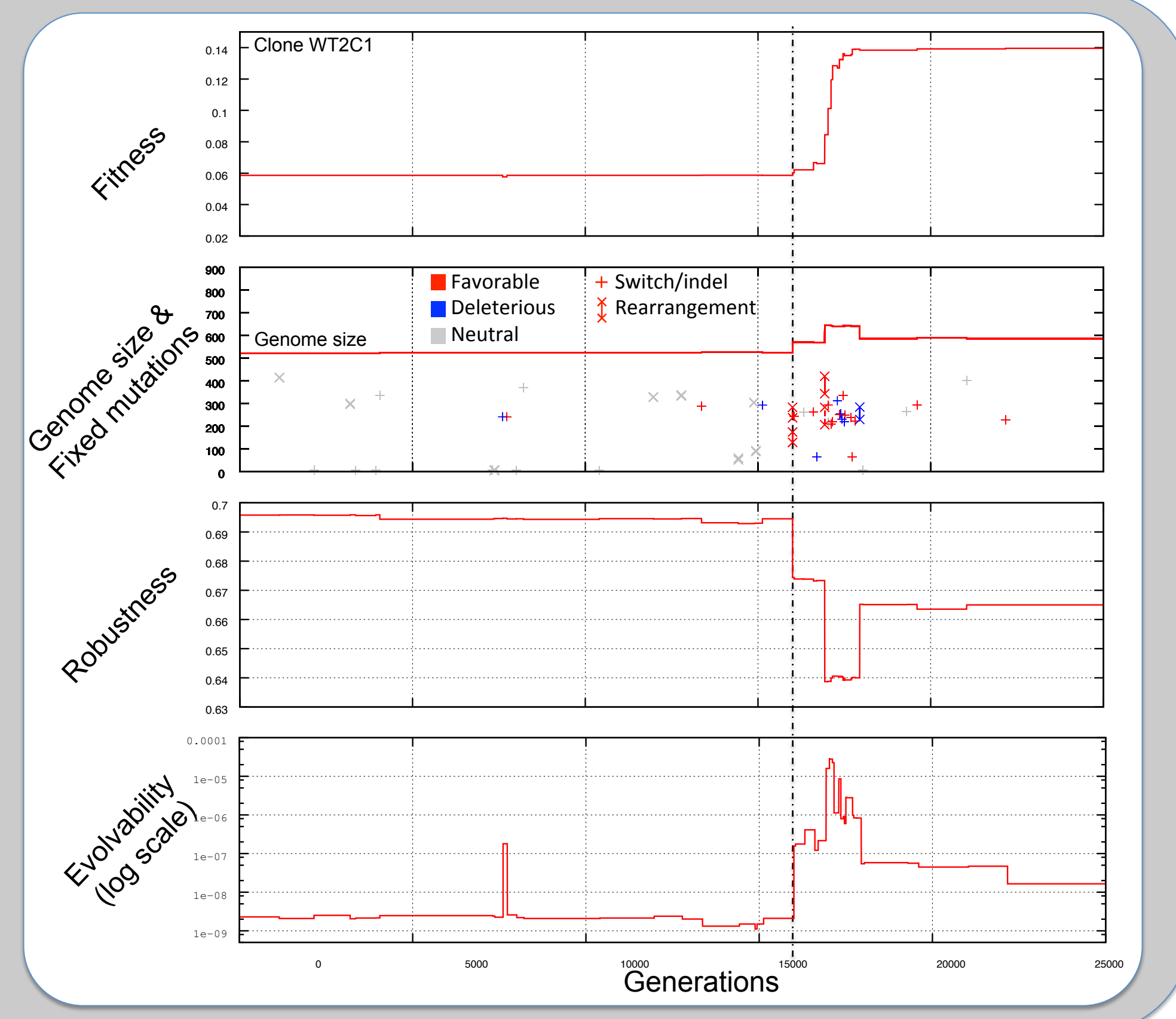
Results (2): innovation dynamics of the clones

Lineage analysis shows that innovation occurs in bursts:

- In 178/215 innovators 80% of the fitness gain occurs in less than 20% of the time (including 68 clones that gain 80% of the fitness in a single mutational event).
- Fixed mutations are not randomly distributed along time (bursts of mutations).

Local sampling of the fitness landscape shows that innovation bursts correspond to very specific regions:

- Areas of low robustness (generally due to genome size increase).
- Areas of very high evolvability: innovations are triggered by mutational events that strongly increase the evolvability of lineages.



Results (3): triggering events

The 215 innovations were triggered by:

- 104 duplications (93 favorable, 10 deleterious, 1 neutral).
- 33 small insertions (19 favorable, 14 deleterious).
- 10 small deletions (all deleterious).
- 11 point substitutions (all deleterious).
- 57 uncharacterized events due to time resolution.

Innovations are often triggered by duplications

	Fixed events	Mean fitness improvement	Mean evolvability improvement	Mean time from previous mutation	Mean time to next mutation
Substitutions	1172	$7.16 \cdot 10^{-4}$	$-4.41 \cdot 10^{-7}$	818	867
Small insertions	916	$9.90 \cdot 10^{-4}$	$-2.98 \cdot 10^{-6}$	1176	940
Small deletions	911	$5.48 \cdot 10^{-4}$	$-4.29 \cdot 10^{-7}$	817	1207
Duplications	168	$4.10 \cdot 10^{-3}$	$2.18 \cdot 10^{-5}$	2175	636
Large deletions	29	$2.57 \cdot 10^{-4}$	$-1.47 \cdot 10^{-7}$	662	850
Translocations	8	$3.18 \cdot 10^{-3}$	$2.58 \cdot 10^{-8}$	3795	2215
Inversions	64	$1.70 \cdot 10^{-4}$	$2.37 \cdot 10^{-7}$	1263	1746

Discussion: the combinatorics of fitness landscapes

In compacted genomes, like viral ones, the combinatorics of point mutations is quickly exhausted. Yet, the combinatorics of rearrangements is much larger and cannot be fully explored in a reasonable time. Duplications open new paths in the fitness landscape and allows for new favorable mutations to occur, leading to bursts of mutations. Hence, the fitness landscape must be considered as more connected at large scale than at short scale. Moreover, considering only point mutations is likely to miss many important evolutionary phenomena, as large-scale rearrangements allow for evolvability bursts that lead to innovations.

	Neighbors in the fitness landscape of WT2C1
Point mutations	521
Small insertions	65 646
Small deletions	3 126
Duplications	141 149 320
Large deletions	270 920
Translocations	140 607 480
Inversions	270 920

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