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Jump then Climb: can rearrangements predict the occurrence of mutational bursts?

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Question: predictability of evolution at the molecular level

- Due to the stochastic nature of mutations, evolution is generally supposed to be unpredictable at the molecular level.
- But mutations are filtered-out by selection which may introduce correlations in the mutational patterns.
- There are many different kinds of mutational events (switches, InDels, rearrangements, HGT...).
- Some of these events may potentiate the occurrence of others, resulting in a non-random fixation.

→ How to study this process?

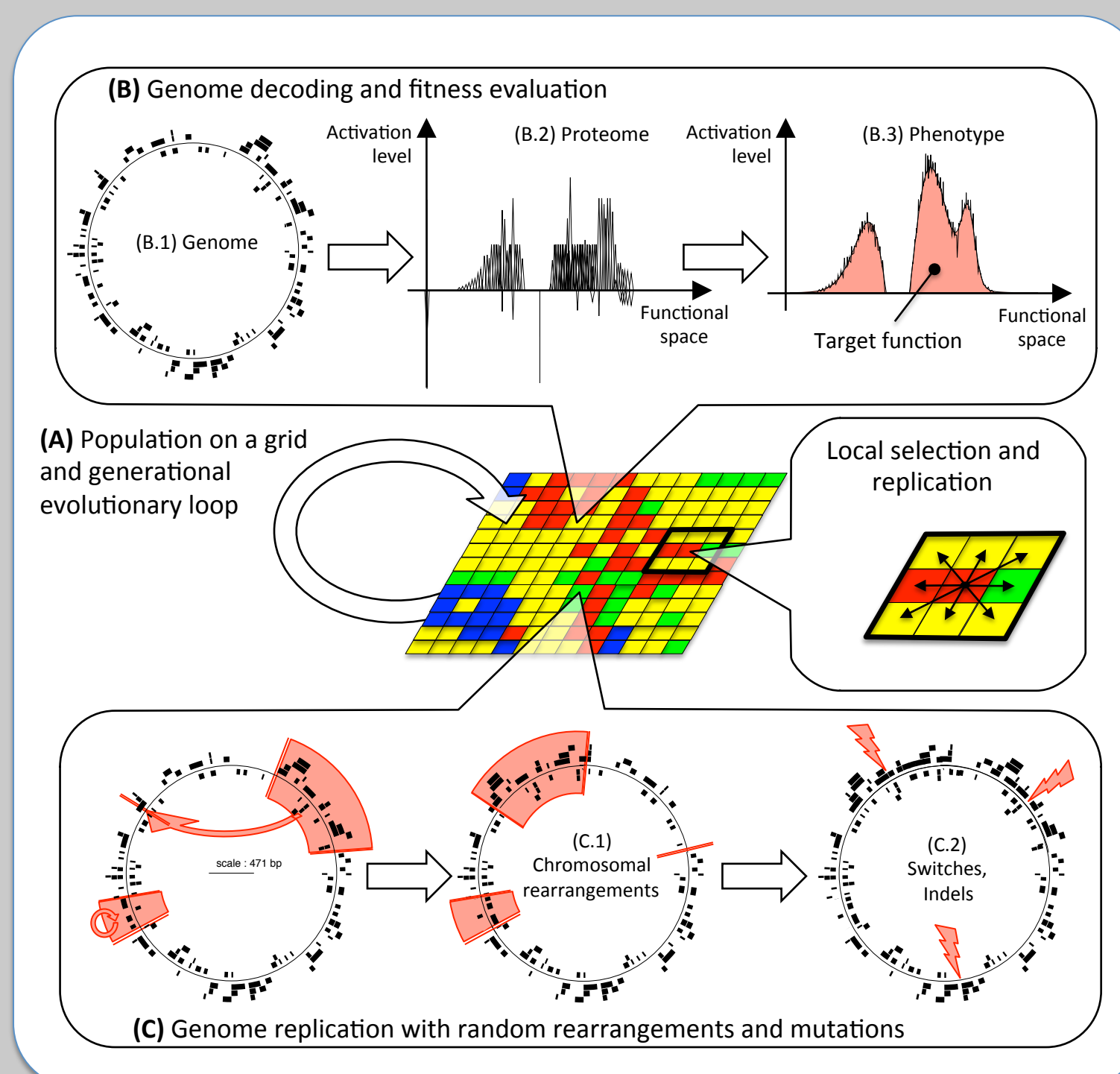
- Modeling and simulation can be used to study how a random spontaneous mutational process can turn into a non-random process when looking at fixed mutations.
- We need a model in which mutational patterns can account for the variety of molecular events that can alter real genomes.
- The model should include a complex genotype-to-phenotype map.
- Both properties are at the core of the Aevol model (www.aevol.fr).

→ Here we used Aevol to test the interactions between the different kind of mutations...

Method: *In Silico* experimental evolution with the Aevol model

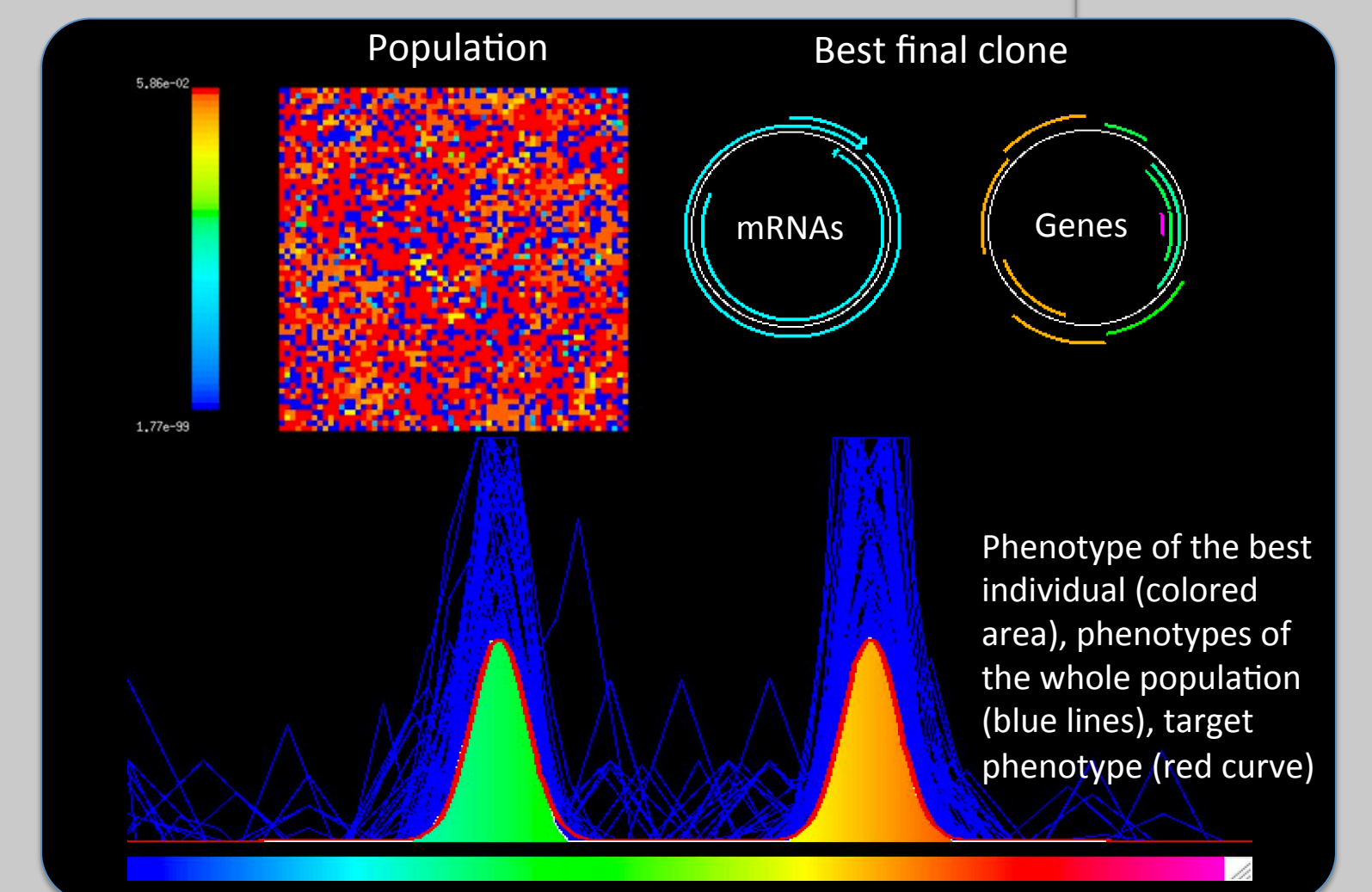
The Aevol model:

Aevol is an *In Silico* Experimental Evolution platform that models microorganisms evolution with explicit selection and replication processes (A). Aevol uses a realistic genome structure (B.1) and a sound genotype-to-phenotype map (B). All functional levels are modeled as mathematical functions (B.2-3). Fitness is computed by comparing the phenotype with a predefined target (in red on B.3). Mutation operators include chromosomal rearrangements (C.1), switches and Indels (C.2).



Experimental framework:

- We evolved 30 viral wild-types by simulating 200,000 generations of evolution under a high mutation pressure (10^{-4} mut.bp⁻¹.gen⁻¹).
- Each WT has been cloned 30x and the 900 clones were further evolved for 30,000 generations.
- We analyzed the sequence of fixed mutations in terms of (1) effect on fitness, genome size, robustness and evolvability (2) waiting time between two mutational events.

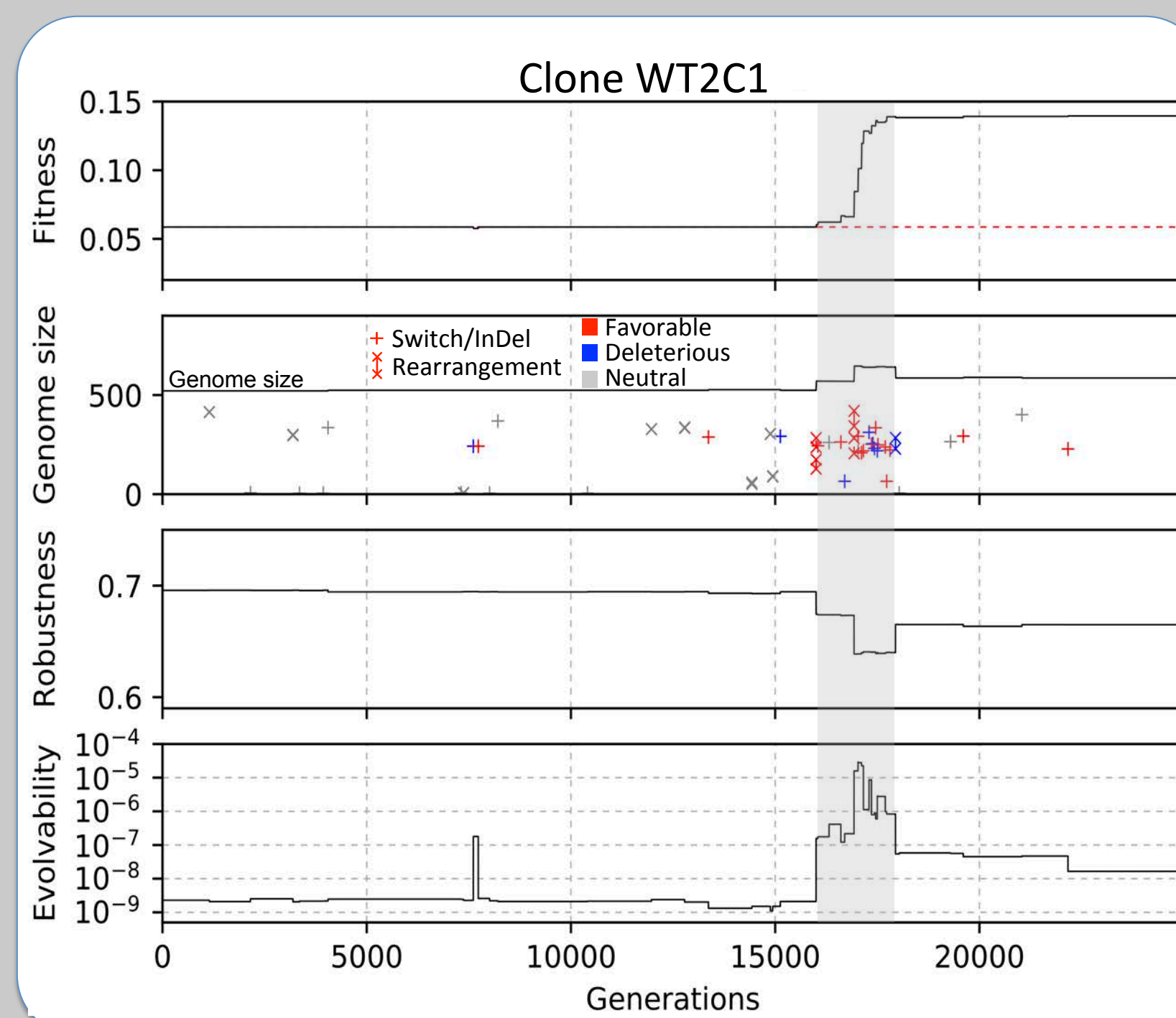


Example of a digital virus WT after 200,000 generations of evolution on the Aevol platform

Results: Random spontaneous events don't fix independently

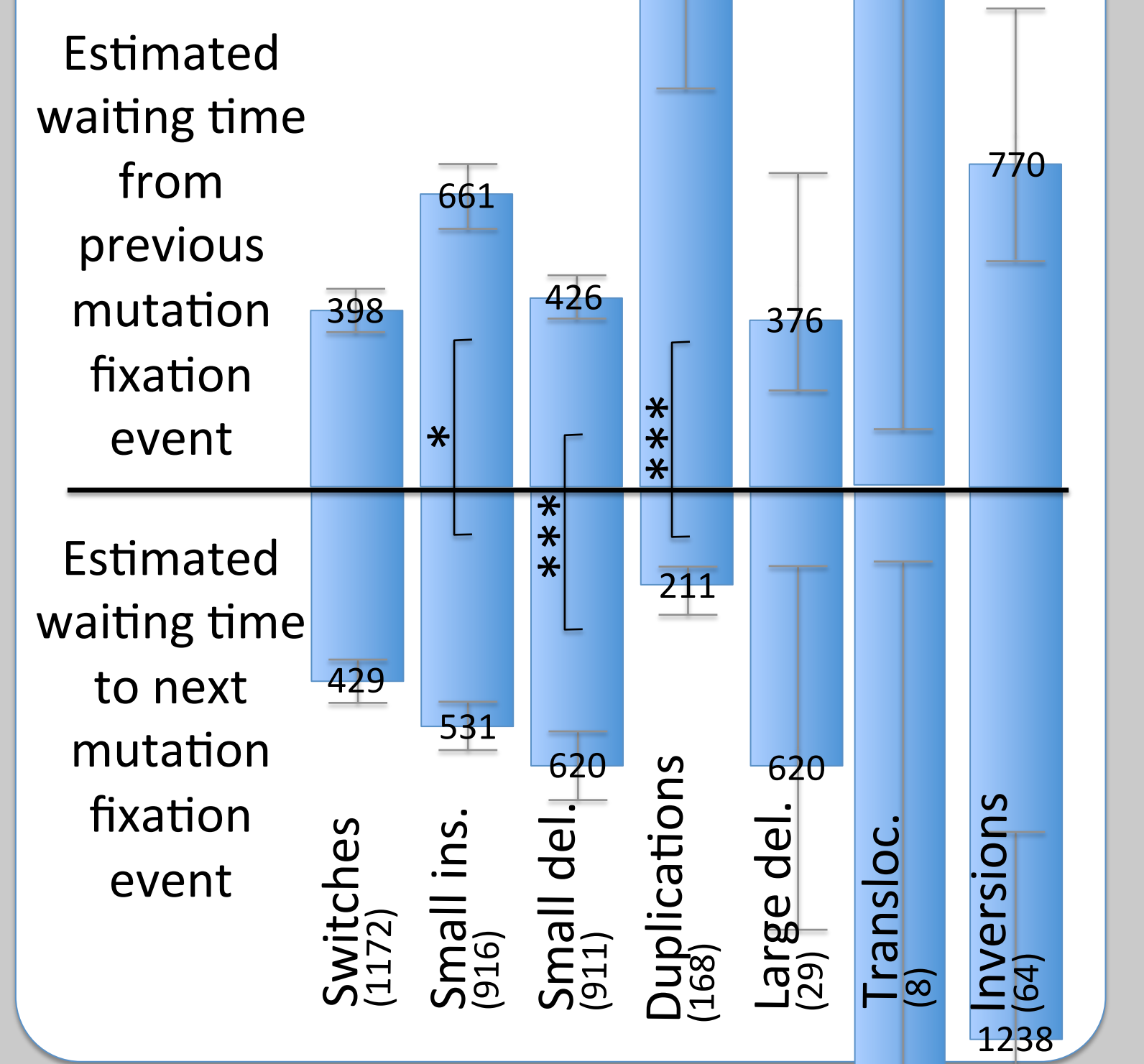
Evolutionary dynamics:

- 215 of the 900 clones significantly improved their fitness.
- Fitness gain often occurs during short mutational bursts with rapid fixation of mutational events.
- These bursts are characterized by a strong increase of evolvability.
- More than 50% of the bursts start with a segmental duplication.
- Compared to spontaneous rates, mutations are rare, except during the bursts.



Waiting time between mutations:

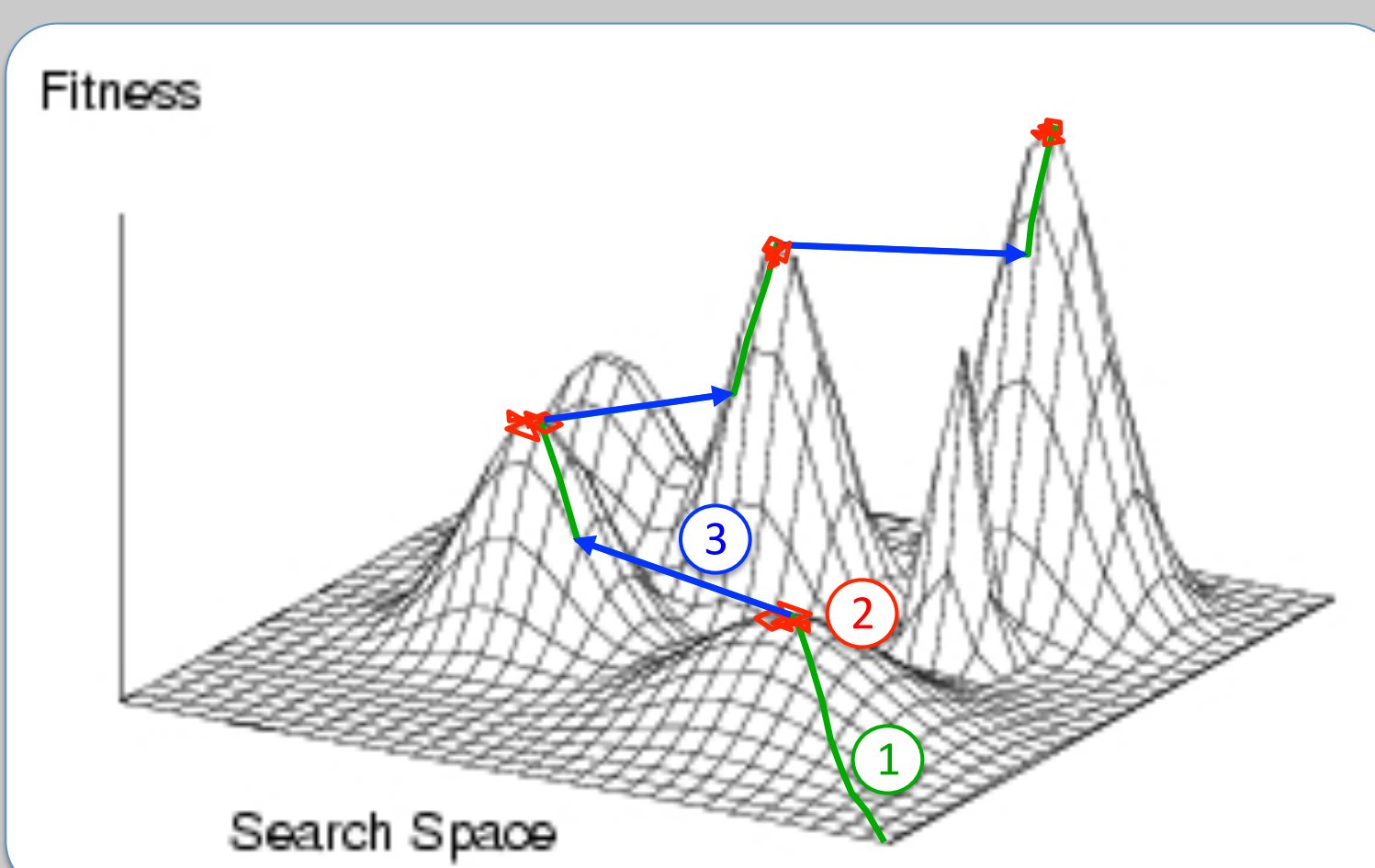
Delays from the previous fixation event (top) and to the next one (bottom) are estimated per kind of mutation for the 215 clones that significantly gain fitness (Hodges-Lehmann estimator). Segmental duplications show a strong skew: they are fixed after a "mutational desert" and are likely to be immediately followed by another mutation fixation event. InDels are also skewed although the skew is less pronounced.



Discussion: Can rearrangements be used as predictor of molecular evolution?

In our experiment evolution proceeds by "jump-and-climb" steps:

1. The viruses climb their local fitness peak. This process mainly relies on substitutions.
2. At the top of the fitness peak, no more favorable substitutions are available. Still many rearrangements remain to be tested.
3. A rearrangement is fixed; viruses jump to a new peak where new favorable substitutions are available. The climbing process starts again.



This sequential process enables partial prediction at the molecular level: fixation of a rearrangement opens the path to new adaptations...

The jump-and-climb process is rooted in the combinatorics of mutational events

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 explored in a reasonable time. When fixed, they open new paths in the fitness landscape that enable fixation of previously impossible point mutations...

Similar processes have been observed in viruses (e.g. Chikungunya) and bacteria (Blount et al., 2012). Our results open three important questions: (1) is this process restricted to short, compact, genomes or can it be generalized, e.g. to cancer evolution? (2) Are there other "jumping" mutational events (3) can these events be used to predict disease emergence or evolution of drug resistance?

| | 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 |