



Evolution of mutator populations in constant environments

Jacob Rutten, Paulien Hogeweg, Guillaume Beslon

► **To cite this version:**

Jacob Rutten, Paulien Hogeweg, Guillaume Beslon. Evolution of mutator populations in constant environments. 2nd EvoEvo Workshop, satellite workshop of CCS2016, Sep 2016, Amsterdam, Netherlands. .

HAL Id: hal-01375669

<https://hal.archives-ouvertes.fr/hal-01375669>

Submitted on 5 Oct 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Evolution of mutator populations in constant environments

Jacob Pieter Rutten^{1,2}, Paulien Hogeweg², Guillaume Beslon¹

¹ Université de Lyon, CNRS, INRIA, INSA-Lyon, UCB Lyon 1, LIRIS UMR5205, Beagle Team, F-69622 Lyon, France

² Theoretical Biology and Bioinformatics Group, Utrecht University, Padualaan 18, 3584 CH Utrecht, The Netherlands

Introduction

The mutation rate of bacterial strains is known to adapt to the evolutionary conditions through the emergence of “mutator strains”. These strains have a 10 to 100 fold raised mutation rate compared to regular individuals [1]. Mutator strains are supposed to raise in specific conditions such as stress or environmental change. Indeed, in such conditions, the elevated mutation rate can be beneficial since it enables bacteria to quickly find a positive mutant. In such a case, the mutator allele hitch-hikes with the favourable mutations and the mutator strains can come to fixation [2]. Now, mutators also experience a mutational burden due to muller’s ratchet. When the environment is stable for a long time this burden will wash-out mutators from the population, leading to the fixation of non-mutator strains [2]. Hence, the dynamic of mutator/non-mutator strains should show bursts of mutator invasion linked to environmental variation.

This view is challenged by the Long Term Experimental Evolution experiment in which 6 out of 12 strains had become mutators and keep a very high mutation rates for tens of thousands of generations [3]. Moreover, in some of these 6 strains, mutators have emerged late in the experiment (e.g. after 20,000 generations). At that time most of the fitness improvement had already been fixed and the benefit of mutators is much less clear than earlier in the experiment. Finally, despite theoretical predictions on mutation rates no slow down of adaptation is observed compared to non-mutator strains, even after thousands of generations [4].

All these observations call for a deeper understanding of mutator strains evolution. To this aim we used the aevol simulation software [5]. In aevol we first evolved 10 Wild-Type populations with parameter setting leading to the evolution of bacteria-like genomes [6]. These populations evolved for 300,000 generations. Then, we cloned each of these populations 20 times and 10 of these clones were evolved with a 100 fold increase of the substitution rate (the rate of all other kind of mutations being kept constant). These clones are later-on called “mutators”. The remaining 10 were evolved with the same mutation rate as the wild-type (controls). The evolution experiments were continued for 100,000 generations and we were then able to analyse the behaviour of the mutators and

to compare it to the controls. Importantly the environment is kept constant all along the experiment.

Results

When compared to the controls, the mutators systematically show a mutational burden that is more or less pronounced depending on the initial strains (figure 1). This burden last for a few thousands of generations. Then the mutators start to recover and most of them regain their initial fitness. Indeed, out of the 100 mutators, 66 have recovered their initial fitness (i.e. the fitness of the ancestral clone at generation 300,000). 25 are doing even better since, at the end of the experiment, they have a net gain in fitness that is higher than the wild-type strains at the same generation (i.e. mutators at generation 400,000 are better than control at the same generation).

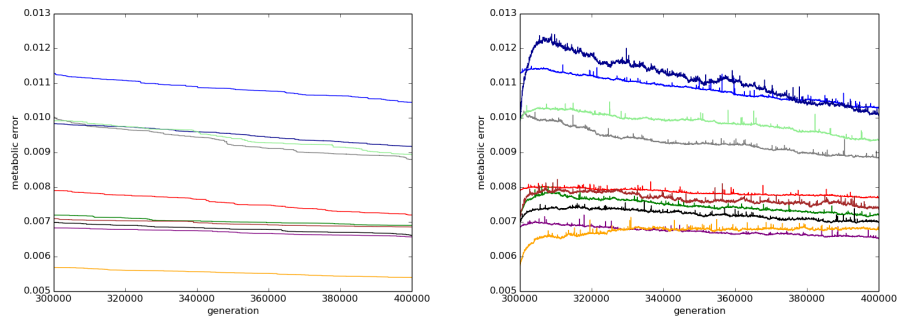


Fig. 1. Mean change in metabolic error of the ancestral lineages between generation 300.000 and 400.000 for the ten replicates of each starting population (the lower the metabolic error, the higher the fitness). Left: Mean change in metabolic error of wild types. After 300.000 years of pre-evolution, we still observe reduction of the metabolic error for all starting populations. Right: Mean change in metabolic error of mutators strains. All 10 populations show an initial increase in the metabolic error, followed by compensatory evolution.

When looking at the evolution of mutators genome, an interesting feature immediately catches the eye. While control genome sizes are almost constant along the 100,000 generations of the experiment, mutators genomes regularly increase, with a final genome length 10% longer than their initial size. This change in genome size is even more striking if one look at the two main compartment of the genome: essential base-pairs versus non-essential base-pairs (in aevol essential base-pairs are nucleotides that cannot be changed or removed without changing the phenotype. On the opposite non-essential base-pairs can be removed without any phenotypic effect). In the control strains, the constant

genome size actually hides a slight increase of the essential bp and a slight decrease of the non-essential bp. On the opposite, in the mutators, the number of essential bp is slightly decreased while the number of non-essential bp strongly increases (the number of non-essential base-pairs being often doubled during the experiment).

To understand the dynamic of the genome increase in the mutators, we developed two analysis tools. First, using the `aevo1_misc_ancestral_robustness` post-treatment, we are able to estimate the evolution of the local curvature of the fitness landscape along the lineage of the best final individual. Second, we developed a Monte-Carlo procedure that enables us to maintain the genome size constant while keeping the same mutational burden³. We then observed that the increase of the genome size leads to an increase of the fraction of deleterious mutants around the ancestor while the fraction of positive mutants remains stable. Indeed, removing the added non-essential bp invert this tendency and reduce the fraction of deleterious mutants.

Discussion

Our results confirm that a sufficient increase of mutation rate results in a mutational burden, although this burden is strongly dependent on the wild-type lineage. However, they also show that this burden can be quickly reduced by the evolutionary adaptation of the mutator strains to the new mutational conditions. Indeed, most mutator strains recovered their initial fitness. More surprisingly, mutators can sometime overcome the wild-type lineage, providing they acquire a genetic structure that enable them to support the mutational load without experiencing the associated burden.

Analysing the genomes of the mutator strains, we have been able to understand how the mutators manage to support the mutation rate increase. First they reduce the number of essential base-pairs in their genomes. Interestingly, this reduction is often neutral – a paradox given the definition of essential base-pairs. Indeed, one of the main feature of the mutator genomes is that they contain less mRNAs (but longer ones). This enables them to reduce the number of essential base-pairs (by suppressing a terminator and a promoter) and thus the mutational burden while keeping the phenotype constant. More surprising is the increase of the non-essential base-pairs in all mutator genomes. Now, as the analysis of the mutational neighbourhood along the mutators lineage shows it, the increase of the non-essential base-pairs increases the fraction of offspring harbouring deleterious mutations as well as the net (negative) effect of these mutations. This effect is due to chromosomal rearrangements which deleterious effect is directly

³ A trivial solution to keep the genome size constant would be to forbid all mutational events that change the genome size – i.e. InDels, large duplications, large deletions. However, this lowers the mutational burden and strongly change the evolutionary dynamics of the mutators. We thus developed a post-treatment where these mutations are fully active but that remove/add the same number of non-essential base pairs to keep the global size constant.

related to the size of the genome, whatever the relative proportions of essential and non-essential base pairs [5,7] . Thus, the increase of non-essential base-pairs is likely to trigger an anti-robustness strategy [8]: increasing the deleteriousness of negative mutants let more room for neutral (or even positive) offspring. These offspring are thus able to reproduce more, indirectly increasing their mutational robustness.

To conclude, our results show that the dynamic of mutator strains is strongly dependent on the evolution of their genomic structure. Indeed, when submitted to high mutation rates for a long-enough time, genome structures adapt to better support the mutational load, eventually suppressing the mutational burden. This raises many questions on the dynamic of mutator strains in nature. Indeed, such strains seem to be pervasive, not only in the Long Term Experimental Evolution set-up but also in natural and clinical isolates [9]. Now, although in our experiments the mutational burden is clearly visible in all mutator strains, one can ask whether such a burden would still be experienced for individuals regularly switching between mutator and non-mutator states. In such a case, the genomic structure of the individuals could adapt to the high mutation rate and avoid the mutational burden. Indeed genomic structures are known to be able to evolve such that quick adaptation to a repeatedly changing environment is possible[10]. In such conditions, even a minor environmental change could results in the fixation of mutator strains since these strains would have the ability to quickly find new beneficial alleles without experiencing the associated burden. Moreover, our results show that, providing they own a robust genomic structure, the mutator strains can evolve as rapidly as WT strains, a situation that perfectly mimics what is observed in the LTEE.

Acknowledgement

This work was supported by the European Commission 7th Framework Programme (FP7-ICT-2013.9.6 FET Proactive: Evolving Living Technologies) EvoEvo project (ICT-610427). The authors want to thank all the partners of the EvoEvo project for fruitful discussions.

References

1. Sniegowski PD, Gerrish PJ, Lenski RE. 1997. Evolution of high mutation rates in experimental populations of *E. coli*. *Nature*, 387(6634):703-705.
2. Tenaillon O, Toupance B, Le Nagard H, Taddei F, Godelle B. 1999. Mutators, population size, adaptive landscape and the adaptation of asexual populations of bacteria. *Genetics*, 152(2):485-93.
3. Barrick JE, Yu DS, Yoon SH, Jeong H, Oh TK, Schneider D, Lenski RE, Kim JF. 2009. Genome evolution and adaptation in a long-term experiment with *Escherichia coli*. *Nature*, 461(7268):1243-7.

4. Lenski RE, Wiser MJ, Ribick N, Blount ZD, Nahum JR, Morris JJ, Zaman L, Turner CB, Wade BD, Maddamsetti R, Burmeister AR, Baird EJ, Bundy J, Grant NA, Card KJ, Rowles M, Weatherspoon K, Papoulis SE, Sullivan R, Clark C, Mulka JS, Hajela N. 2015. Sustained fitness gains and variability in fitness trajectories in the long-term evolution experiment with *Escherichia coli*. *Proc. Royal Soc B: Biological Sciences*, 282(1821):20152292.
5. Knibbe C, Coulon A, Mazet O, Fayard JM, Beslon G. 2007. A long-term evolutionary pressure on the amount of noncoding DNA. *Mol Biol Evol* 24(10):2344-53.
6. Batut B, Parsons DP, Fischer S, Beslon G, Knibbe C. 2012. In silico experimental evolution: a tool to test evolutionary scenarios, *BMC Bioinformatics*, 14 (S15)
7. Fischer S, Bernard S, Beslon G, Knibbe C. 2014. A model for genome size evolution. *Bull Math Biol* 76(9):2249-91.
8. Krakauer DC, Plotkin JB. 2002. Redundancy, antiredundancy, and the robustness of genomes. *PNAS* 99(3):1405-9.
9. Denamur E, Matic I. 2006. Evolution of mutation rates in bacteria. *Molecular Microbiology*, 60(4):820-7.
10. Crombach A, Hogeweg P. 2007. Chromosome rearrangements and the evolution of genome structuring and adaptability. *Mol Biol Evol*, 24(5):1130-9.