

The Dynamics of Super-Mutator Hitchhiking in Asexual Populations . Tanya Singh¹ Paul Sniegowski¹

Department of Biology, University of Pennsylvania, 433 S. University Avenue, Philadelphia, PA- 19104. Philip Gerrish² Department of Biology, University of New Mexico, Albuquerque, NM – 87131.

Introduction: Most mutations are assumed to be deleterious and therefore, a high mutation rate genotype (hereafter referred to as a mutator) is not expected to be favored by selection. However, when the rate of beneficial mutations is sufficiently large, a mutator may hitchhike to high frequency by virtue of being associated with a beneficial mutation¹, especially in an asexual population where it is impossible to lose this association due to complete genetic linkage. Even though this phenomenon has been experimentally elucidated, the threshold beneficial mutation supply rate that favors the fixation of a mutator remains to be quantified, if such a threshold exists.

As a general rule of thumb, the mutator is expected to hitchhike if $u_1 N_1 > u_2 N_2$ (eqn.1) where u_1 and u_2 are the rates at which the mutator and the non-mutator genotypes produce beneficial mutations and the N_1 and N_2 are the sizes of the mutator and non-mutator subpopulations². The rate of beneficial mutations is a function of the genomic mutation rate of the population and the proportion of mutations that are beneficial, which is dependent on the environment that the population occupies. The proportion of beneficial mutations available in a certain environment can be expressed as f_b , or the fraction of total mutations that are beneficial. This proportion is usually assumed to be quite low, (but some evidence supporting a higher proportion of beneficial exists³). We carry out computer simulations to test whether the proportion of available beneficial mutations can influence the fate of a mutator genotype of very strong effect (approximately 4500 fold higher than the wild type mutation rate, hereafter called the super-mutator). In order to simulate a negligible wait time before the first mutation, the mutator individuals in our simulations start with a fitness advantage of 8%. Our simulation data suggest that, even with this initial competitive advantage, a super-mutator lineage fails to increase in frequency, due to a strong influx of deleterious mutations. Although the inequality mentioned above is satisfied in the parameter space that we use for our simulations, the super-mutator fails to fix unless: (1) the first beneficial mutation to arise is of sufficiently large effect or (2) the proportion of mutations that are beneficial is above a threshold ($f_b \sim 0.25$ from our simulations).

Methods: Individual-based simulations model a Wright-Fisher population of $N = 10000$ individuals. Deleterious and beneficial mutations are drawn from a gamma distribution with mean $s_d = 0.03$ (shape param-

eter 0.3, scale parameter 0.1) and an exponential distribution with mean $s_b = 0.03$ respectively. We investigate how f_b (the proportion of total mutations that are beneficial), influences the dynamics of super-mutator hitchhiking. The super-mutator genotype is seeded in at an initial frequency of 0.1%. The beneficial mutation rate of the mutator subpopulation and the wild type subpopulation is 0.3 for the mutator and 0.059 for the wild type subpopulation. Hence, in this parameter space, the mutator is expected to hitchhike since $u_1 N_1 > u_2 N_2$ is satisfied.

Results: The following figure show the frequency trajectories of a mutator lineage that starts at a low frequency (0.001), at different f_b values, and when the effect of the first beneficial mutation that arises (s_{b1}) is 8%. We discuss the implications of these results for the probability of occurrence of a hitchhiking event and the fixation of beneficial mutations in asexual populations.

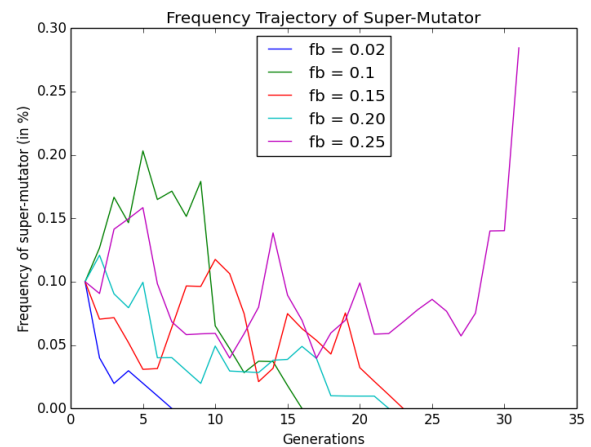


Figure 1: Dynamics of super-mutator hitchhiking under different f_b . This figure represents the change in frequency over time of a super-mutator lineage that starts at a frequency of 0.001 (or 0.1%), at different f_b values. The super-mutator lineage also has a fitness advantage of 8% at the initial time point. The population size is 10000 individuals.

References:

- [1] Sniegowski P.D., Gerrish P.J., Lenski R.E. (1997) Evolution of high mutation rates in experimental populations of *E. coli*. *Nature*. 387(6634):703–70. [2] Chao, L. & Cox, E. C. 1983. Competition between high and low mutating strains of *Escherichia coli*. *Evolution* 37:125-134. [3] Perfeito L., Fernandes L., Mota C., Gordo I. 2007 Adaptive mutations in bacteria: high rate and small effects. *Science* 317, 813–815.