Emergence of Elevated Mutation Rates in Asexual Populations

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The most evolutionarily relevant characteristic that an individual inherits from its parents is the average number of offspring that it will leave, i.e. its fitness. But, is fitness the *only* evolutionarily relevant heritable trait? We show that, in a concrete and biologically realistic setting, the answer is "no".

A mutator is an allele that increases the mutation rate throughout the genome by disrupting some aspect of DNA replication or repair. The elevated mutation rate is heritable and therefore subject to evolution, even though it does not affect fitness in the current generation. Mutators that increase the mutation rate by the order of 100 fold have been observed to spontaneously emerge and achieve high frequencies in natural populations and in celebrated long-term evolution experiments with *E. coli*. Mutator alleles are also implicated in antibiotic resistance and may provide insight into the evolution of cancer.

We developed a quantitative model of mutator dynamics and compared the results to stochastic simulations. This immensely complex process is made tractable with the following assumptions:

1. Beneficial mutations that achieve fixation do so instantaneously.
2. Beneficial mutations that do not achieve fixation are ignored.
3. Deleterious mutations are treated as lethal.

This allows for a complete, though approximate, description of the population in terms of the single variable x = the fraction of the population that are mutators. We solve the resulting model both numerically and analytically. Our model results match those from simulations over the range of parameters that are biologically relevant.

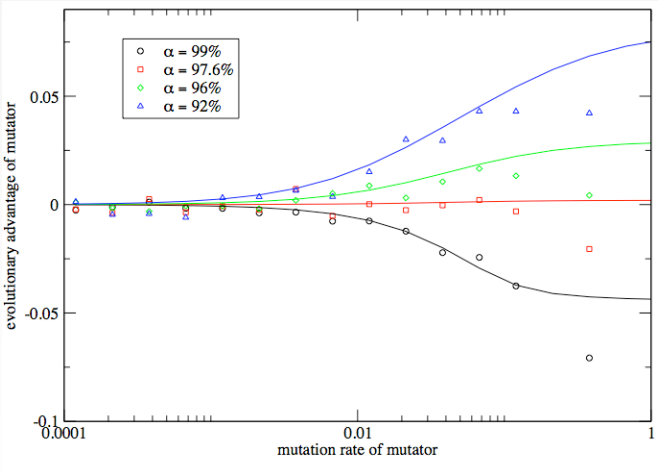

Figure: Comparison of simulations results (points) with model predictons (lines). α measures how adapted the population is to its environment. When α drops below a critical value, there exists a mutation rate for which mutators become favored. Our model predicts this value with impressive accuracy (red curve).

Principle Qualitative Results:

-Mutators suffer the same balance between deterministic and stochastic effects as classical, static mutants.

-Deleterious mutations are irrelevant to mutator success in many parameter ranges

- Mutators are evolutionarily favored in:
  - -Large populations
  - -Harsh environments
  - - Genetic backgrounds with potent mutations (both advantageous and deleterious)

- The evolutionary advantage enjoyed by mutators is always less than the advantage of mutations in the genetic background