Evolution of high mutation rates is generally constrained but permitted during intermediate-level cycles of starvation

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**More results for Experiment II can be found on https://www.biorxiv.org/content/10.1101/865584v1.

INTRODUCTION

What might affect the evolution of mutation rates?
- Biophysical limitation of functional protein complex.
- Mutational load due to the deleterious effects of mutations.
- Linkage effects of beneficial mutations.
- Genetic-drift barrier.

How fast can the evolution of mutation rates happen in different populational-genetic environments?

Can we observe different evolutionary outcomes of mutation rates in different kinds of environment?

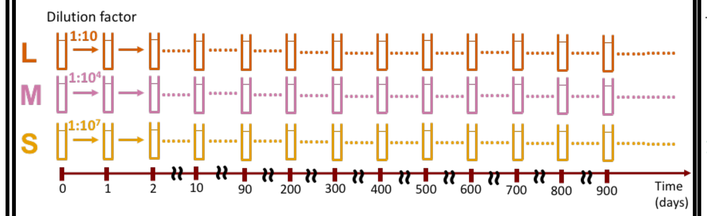
MATERIALS AND METHODS

We evolved *Escherichia coli with* two genetic backgrounds for 900 days.

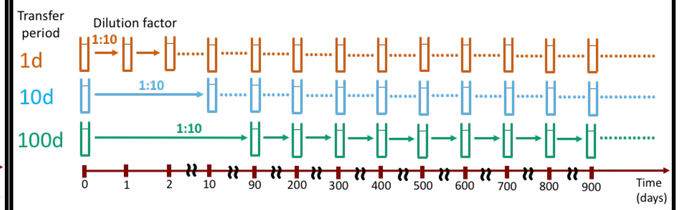
Genetic background	Point mutation rate per clone per generation
MMR−	0.151
WT	0.001

(Lee *et al.* 2012)

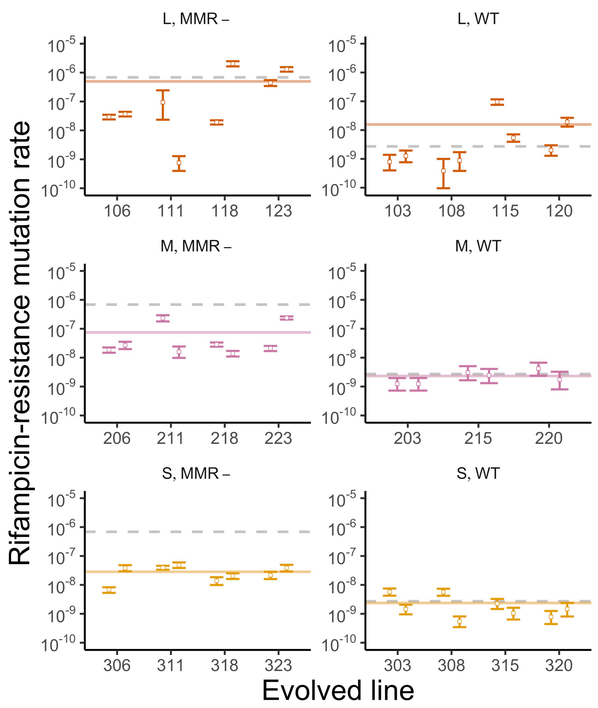
Experiment I: three transfer sizes (TSs) for bottleneck effects



Experiment II**: three transfer periods (TPs) for starving effects

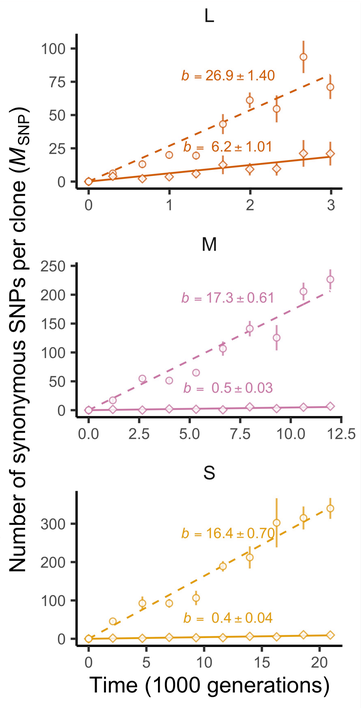


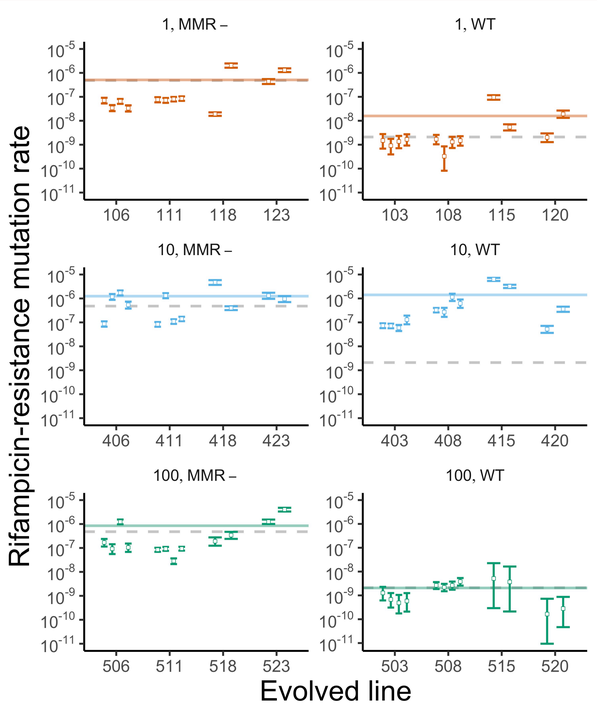
RESULTS



< Figure 1. Evolution of mutation rates in experiment I. Mutation rates were measured by fluctuation tests. For each transfer size and genetic background, three or four parallel lines are reported. Two clones per line were surveyed. Open squares with error bars represent the means and 95% confidence intervals for each clone. Each colored line is the mean mutation rate across evolved lines. Gray dashed lines represent the ancestral mutation rates.

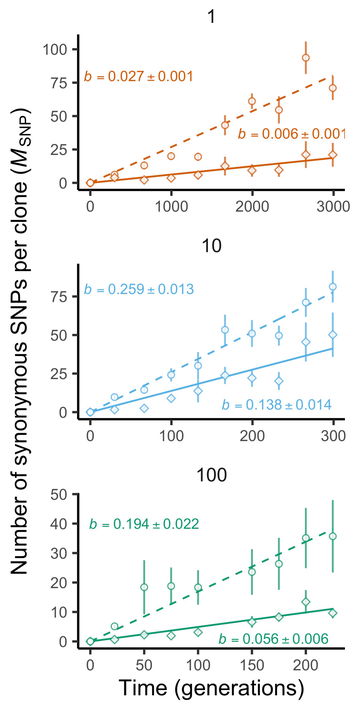
> Figure 2. Tempo of synonymous mutations accumulated in experiment I. The number of SNPs per clone (M_{SNP}) was measured by summed frequencies of all synonymous SNPs. Open circles and diamonds represent the mean M_{SNP} across eight MMR- and eight WT parallel lines, respectively. Error bars are for SE. The dashed and solid line is the linear regression across MMR- and WT lines, respectively (b as slope; SE of b is also shown).





< Figure 3. Evolution of mutation rates in experiment II. Mutation rates were measured by fluctuation tests. For each transfer period and genetic background, three or four parallel lines are reported. At least two clones per line were surveyed. Open squares with error bars represent the means and 95% confidence intervals for each clone. Each colored line is the mean mutation rate across evolved lines. Gray dashed lines represent the ancestral mutation rates.

> Figure 4. Tempo of synonymous mutations accumulated in experiment II. The number of SNPs per clone (M_{SNP}) was measured by summed frequencies of all synonymous SNPs. Open circles and diamonds represent the mean M_{SNP} across eight MMR- and eight WT parallel lines, respectively. Error bars are for SE. The dashed and solid line is the linear regression across MMR- and WT lines, respectively (b as slope; SE of b is also shown).



CONCLUSIONS

In experiment I, most MMR- lines experienced a reduction of mutation rate by 10-100 fold, while WT lines do not. In contrast, in experiment II, we surprisingly found both WT and MMR- lines from the intermediate TP (10) evolved higher mutation rates. These results suggest that the mutational load remains an important factor to constrain the evolution of high mutation rate. However, that constraint can be overcome by extra evolutionary opportunities provided under some special conditions, such as a fluctuating environment of resource availability.

Our collection of pooled-sequencing data also allows us to study genetic basis of the evolution of mutation rates. For example, several structural variations in *mutL* were found in 10-day, WT lines.

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