(Rise and fall of synonymous mutations)

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Abstract

Intrapatient HIV evolution is goverened by selection on the protein level in the arms race with the immune system (killer T-cells and antibodies). Synonymous mutations do not have an immunity-related phenotype and are often assumed to be neutral. In this paper, we show that synonymous changes in epitope-rich regions are often deleterious but still reach frequencies of order one. We analyze time series of viral sequences from the V1-C5 part of *env* within individual hosts and observe that synonymous derived alleles rarely fix in the viral population. Simulations suggest that such synonymous mutations have a (Malthisuan) selection coefficient of the order of -0.001, and that they are brought up to high frequency by linkage to neighbouring beneficial nonsynonymous alleles (genetic draft). As far as the biological causes are concerned, we detect a negative correlation between fixation of an allele and its involvement in evolutionarily conserved RNA stem-loop structures. This phenonenon is not observed in other parts of the HIV genome, in which selective sweeps are less dense and the genetic architecture less constrained.

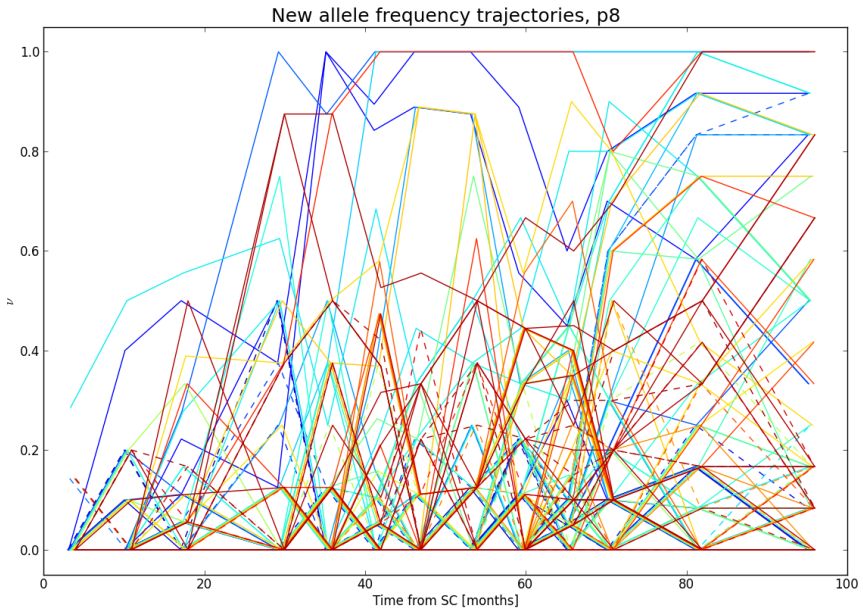

Fig. 1: Allele frequency trajectories of typical patient, C3-V5, nonsynonymous (solid) and synonymous mutations (dashed lines). Most synonymous mutations are not fixed.

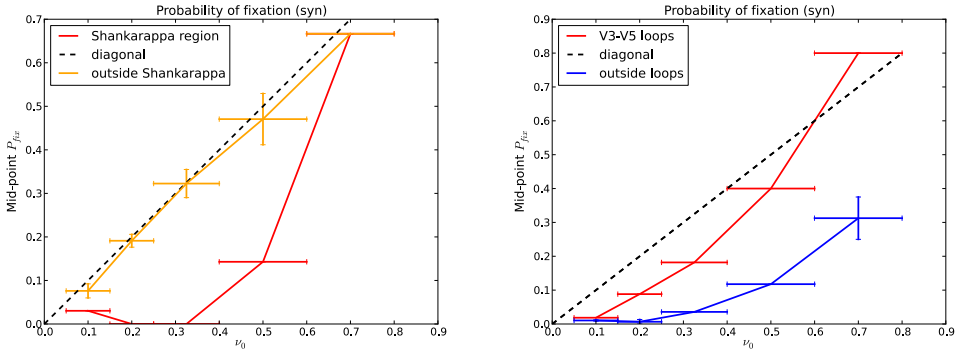

Fig. 2: Fixation probability of derived synonymous alleles is strongly suppressed in C3-V5 versus other parts of the *env* gene (left panel). Especially hard is fixation of new alleles in conserved regions flanking the V loops (right panel). The black dashed line is the prediction from neutral theory, for comparison purposes.

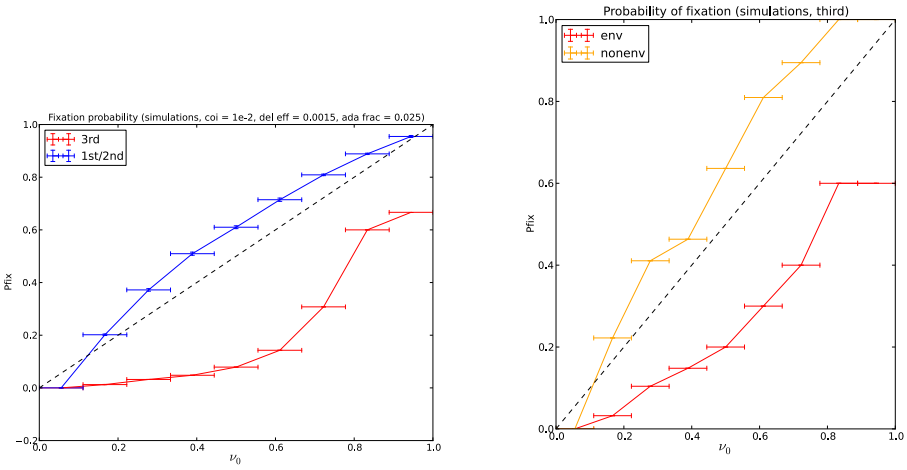

Fig. 3: Simulations show that the suppression of fixation probability can be generated by linkage to sweeping nonsynonymous alleles nearby. Two possible scenarios are competition between escape mutants (left panel) and time-dependent selection due to immune sytem recognition (right panel).

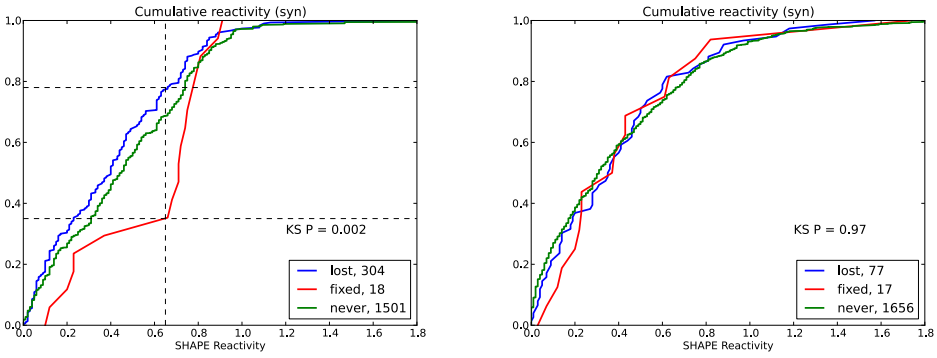

Fig. 4: Watts et al. have measured the reactivity of HIV nucleotides to *in vitro* chemical attack and shown that some nucleotides are more likely to be involved in RNA secondary folds. C1-C5 regions, in particular, show conserved stem-loop structures (Watts *et al.*, 2009). We show that among all derived alleles in those regions reaching frequencies of order one, there is a negative correlation between fixation and involvement in a base pairing in a RNA stem (left panel). The rest of the genome does not show any correlation (right panel). There might be too few silent polymorphisms in the first place, or the signal might be masked by a lot of non-functional RNA structures.

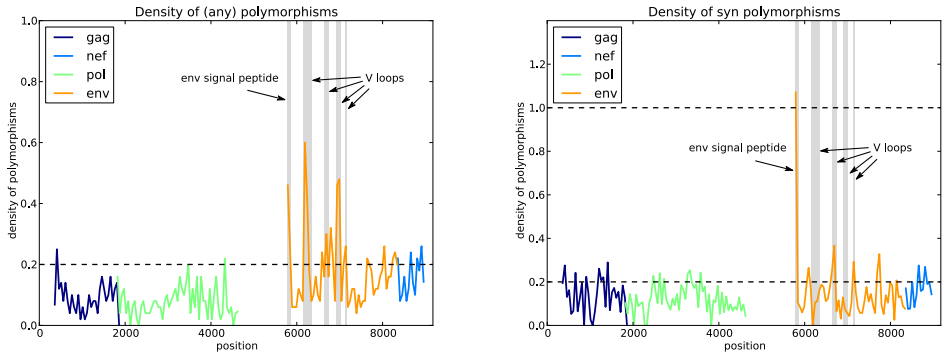

Fig. 5: The total density of polymorphisms (mostly nonsynonymous ones) is highest in the V regions (left panel). The density of synonymous mutations only, however, is not enriched there (right panel). This could be due to a more deleterious effect of synonymous mutations.

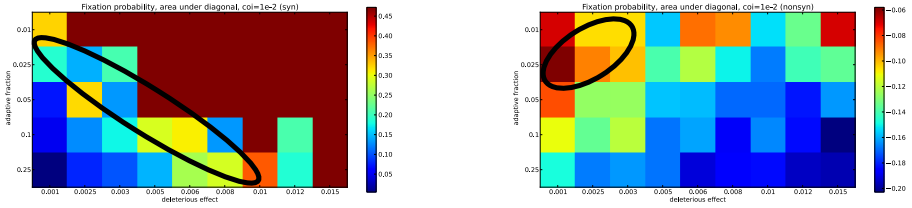

Fig. 6: Simulations on the escape competition scenario show that the density of selective sweeps and the size of the deleterious effects of synonymous mutations are the main driving forces of the phenomenon. A convex fixation probability is recovered, as seen in the data, along the diagonal (left panel): more dense sweeps can support more deleterious linked mutations. The density of sweeps is limited, however, by the nonsynonymous fixation probability, which is quite close to neutrality (right panel). Moreover, strong competition between escape mutants is required, so that several escape mutants are "found" by HIV within a few months of antibody production.

1 Introduction

2 Results

3 Discussion

4 Methods

Acknowledgements

References

Watts, J. M., Dang, K. K., Gorelick, R. J., Leonard, C. W., Jr, J. W. B., Swanstrom, R., Burch, C. L., and Weeks, K. M. (2009). Architecture and secondary structure of an entire HIV-1 RNA genome. *Nature*, **460**(7256), 711–716.