

The rise and fall of deleterious mutation

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Abstract

It is well established that selection is less efficient in small populations than in large ones. Here we review the impact of this effect by considering the gradual selective purging of deleterious mutation over time. We outline an approach to explore the dynamics of this process, and highlight its profound implications.

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1. Introduction

The generation of hundreds of genome sequences over the last decade has led to an emphasis on the saltational processes of gene acquisition and loss as key to understanding bacterial adaptation. Gene inventories are de rigueur for reports describing new genome sequences, and are commonly viewed as a single sample of the genes potentially available to any strain of a given species [29]. The link between gene content and phenotype is often well established, particularly so in those cases where hypervirulence or drug resistance is spontaneously conferred upon formerly mild or manageable pathogens by gene acquisition. The role of gene content variation in adaptive microevolution is also revealed by microarray technology, which provides the means to assay gene content differences within strain samples large enough to be representative of natural populations [9].

In contrast, the gradualistic processes resulting in incremental divergence of the core genome have received less attention [11]. Multilocus sequence typing (MLST), which assays variation within a small sample of the core genome

(~7 genes) in large population samples [32], has provided insights into the population structure and evolution of many environmental and pathogenic species [50] (<http://www.mlst.net>). However, comparative analysis of complete core genomes can also reveal global patterns of mutation bias [48], selection and drift. Here we review recent insights and prospects for comparative core genomics within the framework of the nearly neutral theory. We discuss the broad implications of the short-term accumulation and subsequent purging of deleterious mutations, highlighting the importance of niche restriction and population size. We also outline an approach to compare the dynamics of this process in different populations.

2. Near neutrality and the mutation/drift balance

There are four possible evolutionary fates for de novo point mutations within the core genome. First, mutants may be beneficial and elicit a selective sweep. Second, mutants may impose a severe fitness cost and be very rarely sampled. Third, mutations may be neutral. Fourth, mutations will be neither beneficial, nor excessively harmful, but slightly deleterious. These are by far the largest class; it has been estimated that for every beneficial mutation in *E. coli*, there are 10^5 deleterious mutations [27]. The evolutionary fate of these deleterious mutations will be determined by a combination of selective

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and stochastic forces. Neither extinction nor fixation of these mutants is likely to occur spontaneously, but only after a period of polymorphic limbo where the mutant is present as standing variation in some, but not all, strains in the population [21]. Eyre-Walker et al. suggest that, for eukaryotic populations, the selective consequences of the majority (>70%) of mutations will be sufficiently severe that they are very unlikely to become fixed, whilst ~10% of the mutations will be only slightly deleterious, and these may or may not be fixed [8].

Ohta pointed out that the efficiency of purifying selection in purging these mutations will be the product of the fitness cost of the mutation (the selective coefficient (s), and the effective population size (N_e) [38]. Where $N_e s < 1$ mutants are effectively neutral and the population will evolve predominantly by stochastic drift, but where $N_e s > 1$, selection will act and deleterious mutations will, on average over time, be preferentially purged. Ohta found support for this view from a range of mammalian and drosophilid taxa, and the increased efficiency of selection in large population sizes (or alternatively the increased power of drift in smaller population sizes) has subsequently been confirmed from simulation studies and empirical data [30,39].

A simple means to infer the efficiency of purifying selection is to calculate the per site ratio of non-synonymous to synonymous change (dN/dS , or Ka/Ks). As non-synonymous changes result in an amino acid substitution, they are more likely to be slightly deleterious than synonymous changes (which are more commonly approaching neutrality). The nearly neutral theory predicts that the dN/dS ratio will be greater in smaller populations than large ones, as purifying selection will remove deleterious non-synonymous mutations more efficiently in larger populations. Comparisons of closely related pairs of species, one corresponding to an island (small population) and the other to the mainland (large population) provide a controlled means to examine the effect of N_e . Johnson and Seger examined nine island species of ducks and doves with closely related mainland species [24]. They noted an excess of non-synonymous changes within mitochondrial genes of the island species compared to their mainland relatives, but no difference in the rate of synonymous change. As island species have smaller effective population sizes, so they are less able to efficiently purge slightly deleterious changes, resulting in a higher dN/dS ratio. Woolfit and Bromham compared 70 phylogenetically independent lineages of vertebrates, invertebrates and plants (>600 species) from 19 different island groups [59]. These authors examined nuclear and mitochondrial genes, and also noted a proportionately greater rate of non-synonymous substitutions in the island species.

Given the availability of large volumes of genome data, bacterial populations are in principal ideal to emulate these studies. A central problem lies in the identification of “island” populations and equivalent (closely related) “mainland” populations for comparison. Free passive dispersal and rapid growth by binary fission has led to doubts as to whether truly isolated island populations even exist for free-living microbes [12,37]. Multilocus sequencing studies have been widely

employed to examine the geographical distribution of genotype frequencies of a number of environmental taxa. Although at least partial genetic isolation on the basis of geographical source is apparent in some cases [13,40,55], the promiscuity of gene exchange in bacteria means that geography alone rarely presents a barrier to gene flow [37]. Furthermore, as recently discussed by Lynch, the effective population sizes of prokaryotes are generally much larger than eukaryotes, meaning that purifying selection is on the whole far more efficient, and can elegantly account for the selective maintenance of small (“streamlined”) genomes and operons in prokaryotes [31].

A rare example of ecologically isolated free-living prokaryotic populations was presented by Escobar-Paramo et al. [7]. They used MLST data to compare populations of the hyperthermophilic archaeon *Pyrococcus*, a marine species adapted to growth around hydrothermal vents at temperatures >70 °C. These populations are separated by many miles of inhospitably cold water and the MLST data confirmed their genetic distinctness. A high frequency of deleterious mobile insertion sequences (IS elements) was noted, and the accumulation of these deleterious elements was inferred to be a manifestation of weakened selection due to a small N_e [31,36]. However, unlike the eukaryotic island populations discussed above, no closely related “mainland” population is available for comparison; thus the causal link between ecological “islands” and the accumulation of IS elements remains equivocal.

3. Eukaryotic hosts as islands

Intimate co-evolutionary associations between bacteria and eukaryotes, resulting in intracellular parasitism or mutually obligate endosymbiosis, have evolved independently in many different bacterial taxa. Host-associated bacteria are thought to have evolved from free-living generalist species. The extreme niche restriction and ecological isolation resulting from these ecological shifts correspond to a dramatic decrease in N_e . In the case of maternally (vertically) transmitted obligate endosymbionts of insects (where host progeny are infected via the mother’s ovaries), this effect is reinforced by bottlenecks at every host generation, such that N_e of the bacteria begins to approach that of its host [3].

Consistent with predictions from the Nearly Neutral Theory, genome sequences recovered from endosymbionts reveal striking footprints of increased deleterious change owing to drift. As for the island bird populations, genomes of the genus *Buchnera* (an obligate endosymbiont of aphids) show a markedly higher proportion of non-synonymous changes than their closest free-living (“mainland”) relatives, for example *Escherichia coli* [54]. Woolfit and Bromham presented an ambitious study on 13 phylogenetically independent comparisons of bacterial and fungal endosymbionts with their closest known free-living relatives [58]. This study confirmed an increase in substitution rate in the endosymbionts, again consistent with increased drift, although much of the data was limited to 16S gene sequences rather than whole genomes. Other features of endosymbiont

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