Quick guide

Genetic drift

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What is genetic drift? Say you have a population of 5,000 people. That makes 10,000 copies of each gene. Imagine a gene where 3,000 of those copies are of one particular allele or type. In the next generation, there won't necessarily be exactly 3,000 copies again. There may be 3,050 or 2,960 copies instead. Some gametes get randomly picked out of all the possible gametes that could have been used. This is a bit like tossing a coin, and 100 coin tosses rarely yield exactly 50 heads. Natural selection happens when individuals developed from certain gametes are more likely to survive and reproduce. Genetic drift, together with mutation and recombination, randomly produces the gametes that selection can act on. Or, if there is no selection, allele frequencies can change by mutation and genetic drift alone.

Does genetic drift make much difference to evolution? In some generations the allele frequency goes up, in other generations it goes down. Over the long run, the two mostly cancel each other out. But if an allele frequency hits zero, then the next generation of genetic drift cannot cancel that out. That allele stays extinct, unless it appears again by mutation. So, genetic drift could be important in determining whether a new mutation is lost, or whether it instead becomes common enough for selection to determine its fate. In theory, in a small enough population genetic drift could also be important even for common alleles. The effect of genetic drift over a given time declines exponentially with increasing population size (Figure 1).

Can genetic drift be tested in the lab? In one experiment, Peter Buri evolved over 100 populations of *Drosophila*, randomly choosing only eight males and eight females to breed in each of 19 generations. All the populations started with a 50% frequency of an eye color mutation. In half the populations, the allele frequency went up, in half it went down. In other words, the allele was not under selection, allowing him to test for genetic drift. According to the theory of genetic drift, the variance in allele frequency across the populations should increase by a factor of $p(1-p)/2N$ each generation, where p is the current frequency and N is the population size. Buri plotted the change in allele frequency as a function of p, and got a curve with the right shape, but for N_e = 11.5 rather than N = 16. N_e is called the 'effective population size'. The fact that it is low means that allele frequencies changed faster than expected.

Can genetic drift be tested in natural populations? If you sample two individuals from the same population, the average number of sequence differences at drifting sites should be $4\mu N$, where μ is the mutation rate, which can be measured independently. When we do this for mutations that we think are neutral, we calculate effective population sizes that are much lower than we would expect. What is more, the range in effective population sizes across different species is also much less than we would expect.

Why are effective population sizes so low and so similar? If the size of a population fluctuates over time, then genetic drift is dominated by the smallest size (bottleneck) that the population experiences. Effective population sizes are also lower if random success comes in rare 'jackpots' of many surviving offspring at once, rather than through more frequent success at producing a smaller number of surviving offspring. Perhaps most importantly, even if a mutation has no effect on fitness, it may be on the same chromosome as other mutations that do. There is both background selection against linked deleterious mutations, and 'hitch-hiking' on positive selection for linked beneficial mutations. Allele frequencies can change much faster over time because of linkage to selected sites than because of genetic drift, creating an apparently low population size. When a population goes through a bottleneck, selection at linked sites can be especially important. Most populations carry many recessive deleterious mutations, each of which is rare. During a sudden bottleneck, a small number of those mutations become much more common. Inbreeding now creates homozygotes with two copies of the mutation. This would generate lots of background selection at other sites on the same chromosome. For example, if Buri's eye color mutation was on the same chromosome copy as a recessive mutation, selection would make both mutations less common. If the eye color mutation was on the other copy of that chromosome, selection would make it more common.

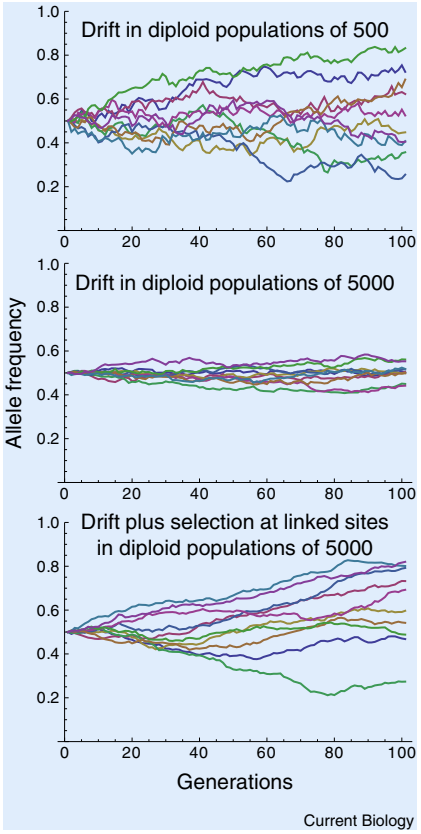

Figure 1. Drift and allele frequencies. Simulated allele frequencies in replicate populations. Drift happens faster in small populations (top panel) than larger ones (middle panel). Selection at linked sites (bottom panel) also increases the speed of change, but is not identical to a small population size (top panel).

OK, but isn't drift still important for rare alleles, even in large populations? Perhaps, but selection at linked sites also affects rare alleles, whether they are neutral or under selection. For example, whether a beneficial new mutation appears randomly in a good genetic background rather than a bad one may be more important than genetic drift in determining whether that allele persists.

So long as allele frequencies change randomly, does it matter why? It would be nice if it didn't matter. In that case the effects of selection at linked genes could be summarized by one number, the effective population size N_e. That

number may not be closely related to the actual number of individuals, but the mathematical theories of genetic drift could still work. But unfortunately, the randomness associated with recombination has different mathematical properties to the random sampling of gametes (Figure 1). With background selection or hitchhiking, if an allele frequency increases in one generation, it is likely to increase again in the next. This is because recombination does not completely mix things up every generation. With genetic drift, what happens in one generation has no connection to what happens in the next. Successive generations of genetic drift mostly cancel each other out, so that over the long term, an allele undergoing genetic drift has much less variation in its success than it would if it were linked to other genes under selection.

Do these differences matter? If genetic drift is not important, then evolution doesn't depend so much on population size. The two theories also predict different distributions of allele frequencies. There may be many more consequences that we don't know about yet: the theory of selection at linked sites is still being worked out.

Can we test whether drift is less important than selection at linked sites? To test this directly in a setup like Buri's, one could look for a correlation between one generation and the next in terms of the magnitude and direction of change in allele frequency. In natural populations, there is lots of indirect evidence supporting the view that selection at linked sites is more important than genetic drift. For example, it is otherwise very hard to explain why patterns of genetic variation depend so little on population size, and so much on differences in the recombination rate along the chromosome.

Where can I find out more?

Barton, N., Briggs, D.E.G., Eisen, J.A., Goldstein, D.B., and Patel, N.H. (2007). Evolution. Cold Spring Harbor Laboratory Press. pp. 413–420.

Buri, P. (1956). Gene frequency in small populations of mutant *Drosophila*. Evolution *10*, 367–402.

Gillespie, J.H. (2001). Is the population size of a species relevant to its evolution? Evolution *55*, 2161–2169.

Hahn, M.W. (2008). Toward a selection theory of molecular evolution. Evolution *62*, 255–265.

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Right temporal TMS impairs voice detection

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Functional magnetic resonance imaging (fMRI) research has revealed bilateral cortical regions along the upper banks of the superior temporal sulci (STS) which respond preferentially to voices compared to non-vocal, environmental sounds [1,2]. This sensitivity is particularly pronounced in the right hemisphere. Voice perception models imply that these regions, referred to as the temporal voice areas (TVAs), could correspond to a first stage of voice-specific processing in auditory cortex [3,4], after which different types of vocal information are processed in interacting but partially independent functional pathways. However, clear causal evidence for this claim is missing. Here we provide the first direct link between TVA activity and voice detection ability using repetitive transcranial magnetic stimulation (rTMS). Voice/non-voice discrimination ability was impaired when rTMS was targeted at the right TVA compared with a control site. In contrast, a lower-level loudness judgement task was not differentially affected by site of stimulation. Results imply that neuronal computations in the right TVA are necessary for the distinction between human voices and other, non-vocal sounds.

The human voice carries important non-linguistic messages about the emotional state, identity or gender of a speaker. This information is essential for everyday social interaction and thus makes vocal sounds the most common and meaningful of our environment. Neuroimaging studies have identified regions along the middle and anterior part of the STS with a preferential neural response to vocal compared to non-vocal sounds (the TVAs) [1]. Their early development [5], ancient phylogenetic history [6], and crucially, preferential response to vocalisations, even those devoid of linguistic content [1,7], suggest that the TVAs might constitute a critical node of the cerebral network involved in voice cognition abilities. However, the exact functional role of the TVAs and, particularly, whether their greater fMRI response to voice indicates a specific role in cerebral voice processing, remains unclear. Our aim was to test a causal link between the right TVA and the ability to discriminate voices from other sounds. To this end, we first localised the right TVA in each subject with

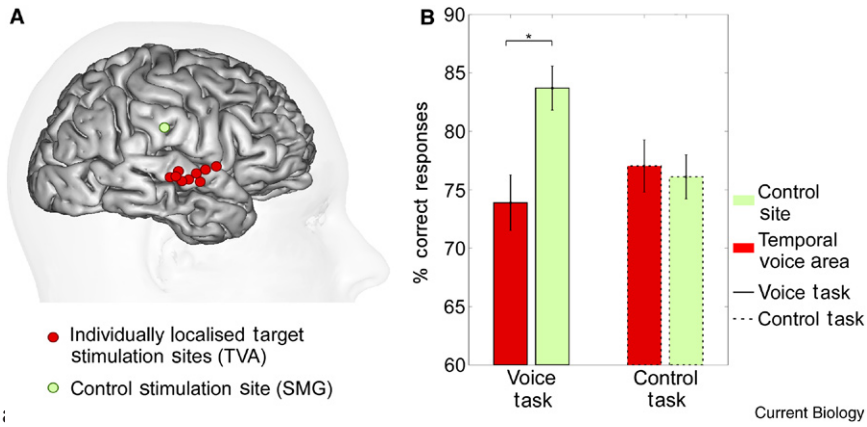

Figure 1. Functional role of the TVA in voice/non-voice discrimination.
(A) Illustration of stimulation sites. Individually localised right temporal voice area (TVA) in red; control site (supramarginal gyrus, SMG) in green. (B) Bar graph illustrates results of both tasks when stimulating the TVA or the control site. Stimulating the TVA caused significantly poorer performance compared with the control site on the voice/non-voice discrimination task. The control task was not affected by rTMS at either stimulation site. Error bars represent standard error of the mean.