FST (as well as related measures such as Gst) has long been used both as a measure of the relative amount of genetic variation between populations and as an indicator of the amount of gene flow among populations. Unfortunately, FST and its clones are also sensitive to mutation, particularly when the mutation rate per locus is greater than the migration rate among populations. Relatively high mutation rates cause estimates of FST and Gst to be much lower than researchers sometimes expect, when migration rates are low in the studied species. Several recent suggestions for dealing with this problem have been unsatisfactory for one reason or another, and no general solution exists (if we are not to abandon these otherwise useful measures of differentiation). In an important article in this issue, Jinliang Wang (2015) shows that it is possible to identify whether the genetic markers in a given study are likely to give estimates of FST that are strongly affected by mutation. The proposed test is simple and elegant, and with it, molecular ecologists can determine whether the FST from their makers can be depended on for further inference about their species’ genome and the demographic forces which shaped its patterns.

Keywords: bias, FST, Gst, population differentiation

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Almost a century ago, Wright (1943) proposed a measure of the patterns of genetic variation across individuals and across populations. His FST tracked the variance in allele frequency among populations, as standardized by mean allele frequency. This measure had the advantage of seeming to be independent of that mean allele frequency, so that it might give a similar number for all (neutral) genes in the genome.

After the development of more readily available genotyping technology, first through allozymes and later microsatellites and now DNA sequences, FST became a very important tool in describing spatial population genetic patterns. As its use increased, the statistics of FST became more sophisticated, with corrections for sample size [e.g. Weir & Cockerham (1984)] and adjustments for more than two alleles per locus [e.g. Gst, Nei 1973].

In the original articles by Wright exploring what factors might affect the genetic differentiation of populations, he considered genetic drift, migration among populations, and mutation. He showed that drift tends to increase the differentiation of populations, while migration and mutation tend to make FST smaller. However, when these ideas were applied to allozyme data in the 1960s and 1970s, migration was believed to occur at a much greater rate than mutation, and the effects of mutation on FST tended to be ignored. FST came to be viewed as an index that revealed something about the balance between drift and migration. This was usually a legitimate interpretation in the era of allozymes.

However, as microsatellites became the most commonly used genetic markers in evolutionary genetics and molecular ecology, mutation may more plausibly play a strong role relative to migration. Microsatellites (especially the more variable ones that tend to be chosen for population-level studies) have much higher mutation rates than allozymes, for their measureable phenotypes. Old views of how FST ought to ‘behave’ became misinformed. Loci that experience a high level of mutation relative to migration will tend to have low FST (or Gst), even though migration rates are low. Thus, a broader range of taxa than before may have observed low Gst values even in species with extremely limited migration rates. This difficulty arises because FST and Gst are relative measures; they give values that are proportional to the amount of genetic differences between populations, as standardized by the total genetic variance or the genetic diversity within demes. As a result, when mutation rates are high, the probability that two alleles are different within a population grows large, capping the value of maximum possible FST. Another way of thinking about it is that mutation erases the history information at a locus; if mutation occurs at a higher rate than migration, a single site will have little signal left in the data from the effects of migration.

This difficulty – that FST or Gst would return low values with significantly limited migration – was recognized early on. Wright’s equations clearly showed the role of mutation on FST. Others pointed out the sensitivity of FST measures to mutation (Nagylaki 1998; Balloux and Lugon-Moulin 2002, Hedrick 1999), but these issues were perhaps not broadly enough appreciated. Some relatively recent estimators have been proposed to correct this problem (Hedrick 2005; Jost 2008), but these measures have not been proven to be successful in returning the biological information we seek from differentiation statistics (Whitlock 2011; Wang 2013). So we are left with the unsatisfying situation where
a classic index is known be very useful in some circumstances but not others, and the alternative measures do not track the information about population demography that we need.

Given this background, the article by Wang (2015) in this issue is a welcome addition to this literature. Wang shows that we can plot the $G_{ST}$ of a locus against its diversity ($H_S$), and in so doing discover whether these loci are likely unbiased predictors of the relative coalescent histories of the genome. He shows that for loci over which there is approximately the same $G_{ST}$ over a range of $H_S$ in intraspecific comparisons, $G_{ST}$ can be useful for comparing across loci, across populations and across species. On the other hand, when $G_{ST}$ is strongly correlated with $H_S$, $G_{ST}$ will carry little useful information about the demographic history of the population. Wang provides software that allows such comparisons to be made easily, and he applied it to several published data sets (see, e.g., Fig. 1).

This approach is elegant, simple and likely to provide (perhaps for the first time) reliable guidance to the empiricist. All studies which measure $F_{ST}$ or $G_{ST}$ ought to ask whether the loci they use, in the species they study, are reliable indicators of genomewide parameters using Wang’s approach. The data required are simple enough that this approach ought to also provide a way to retrospectively ask how reliable are $G_{ST}$ measures from previously published data. I fear that an unfortunately large fraction of published results based on microsatellites may not meet this reasonable standard. As the field moves more towards the analysis of SNPs, the mutation rate per site should be low enough that this difficulty of a mutation ‘bias’ should not be a great issue. In any case, Wang’s elegant new method ought to be able to detect situations that are likely to show this bias in inference from $F_{ST}$ or $G_{ST}$.

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Fig. 1 The Atlantic salmon (A) has patterns of $G_{ST}$ and within-population heterozygosity that suggest that its SNPs might on average give reliable information about its demographic past, but a large fraction of the microsatellites scored in this population show the evidence of $G_{ST}$ being downwardly biased by high mutation (see figure 5A and B in Wang 2015). $G_{ST}$ from microsatellites is similarly unreliable in bluenose sharks, Mediterranean shore crabs (B), and blacktip shark populations, but $G_{ST}$ could be relied upon for demographic inference in copper rockfish (C) populations. Photograph credits: (A) ‘A salmon jumping at Murray’s Cauld, Philiphaugh’ copyright Walter Baxter, licensed under CC BY-SA 2.0 (photograph cropped). (B) George Chernilevsky, public domain. (C). Chad King (SIMoN/MBNMS), public domain.