There are many assertions in Jamieson and Allendorf’s recent review in TREE [1] (JA2012) that are either incorrect, or contradict current knowledge, the material they cite (especially [2–4]), or their own publications [4–6]. Their review also includes contradiction and misrepresentation of published work. Given space and citation constraints, here we only address some key issues, and reference mainly reviews.

Erroneous attribution
JA2012 claimed that Spielman et al. [7] ‘noted that the reduced heterozygosity made no direct contribution to the current threatened status of any of the taxa in their study.’ In fact, we wrote ‘We were unable to determine whether genetic factors have contributed to the current threatened status of the taxa in our study.’ [7].

Misrepresentations of the relation between genetic factors and extinction
JA2012 also stated ‘the conclusions drawn by Spielman et al. clearly confound correlation with causation: that is, lower genetic diversity does not necessarily equate to elevated extinction risk.’ However, we stated ‘Each of the essential links between reduced genetic diversity and subsequent extinction risk has been verified’ [7], and followed with multiple, independent lines of supporting evidence. Similarly, Jamieson et al. [5] wrote ‘Empirical studies have confirmed direct links between inbreeding and/or loss of genetic variation and population viability…’.

JA2012 stated that ‘estimates of reduced heterozygosity in populations of conservation concern should be linked directly to estimates of reduced fitness associated with inbreeding depression before invoking increased extinction risk due to genetic factors’. There is already extensive theoretical and empirical evidence for such links in many circumstances, as documented in [7] and elsewhere [2,3,5].

Predicted links
Theory predicts causal links between neutral genetic diversity, genetically effective population size ($N_e$), and inbreeding coefficient ($F$) in closed random mating populations [2–4,7] (Equation 1):

$$
\frac{H_t}{H_0} = \left(1 - \frac{1}{2N_e}\right)^t = 1 - F
$$

where $H_0$ is initial heterozygosity and $H_t$ is heterozygosity after $t$ generations. Because $F$ is causally related to inbreeding depression for reproductive fitness [2–4,7], this links heterozygosity and inbreeding to fitness. Census population size ($N_c$) is also linked when $N_c$ and $N_e$ are positively correlated [8].

Empirical tests support these predictions
First, ‘inbreeding depression is a universal phenomenon’ (Allendorf and Luikart [4]). Second, $N_c$ and $N_e$ are correlated with genetic diversity for allozymes, microsatellites, and major histocompatibility complex (MHC) variation [3,8]. Third, genetic diversity and fitness are positively correlated across populations [2,3,7,8]. Fourth, inbreeding increased extinction risk in experiments where other causes were excluded or controlled [2,3,7]. Fifth, inbreeding substantially reduces median times to extinction in wild populations, based on population viability analyses for well-studied species [2,3,7]. Sixth, inbreeding increased extinction risk in natural habitats in the three species where this was seriously examined [2,3,7]. Seventh, loss of alleles at self-incompatibility loci (S-alleles) reduced fitness in self-incompatible plants [2–4]. Indeed, the Illinois lakeside daisy was effectively extinct due to low S-allele diversity, but recovered following outcrossing [2,3]. Eighth, reduced genetic diversity at the sex locus in Hymenoptera elevated predicted extinction risk [3,4].

JA2012 stated ‘they [7] provide no empirical evidence that the threat status of the populations or species they analyzed would be diminished if their genetic diversity was somehow enhanced.’ We [7] wrote ‘small natural populations of a topminnow fish, a greater prairie chicken, and a Swedish adder all have declined in numbers, in part because of inbreeding, and recovered after outbreeding.’ Indeed, outcrossing inbred populations to unrelated conspecific populations with the same karyotype and environmental adaptations usually enhances fitness, as documented by Darwin, plant and
animal breeders, and studies of laboratory and wild populations [2,3,9].

JA2012 incorrectly concluded ‘the contention that there is evidence of a clear and unambiguous link between \( N_e \) (or \( N_c \)), evolutionary potential, and extinction risk remains unsupported in the literature.’ Theory predicts such links [2,3] and they are supported empirically [10]. We [7] stated ‘reduced genetic diversity has been shown to reduce times to extinction under changing environments’, and similarly Allendorf and Luikart [4] said ‘loss of genetic variation due to inbreeding made these lines [10] less able to adapt to continuing environmental change.’ Similarly, Jamieson et al. [5] concluded ‘inbreeding in small populations almost invariably leads to loss of genetic variation, and such populations are less responsive to selection pressure.’ Furthermore, species that evolved heavy-metal tolerance when repopulating polluted areas in Wales had pre-existing genetic variation for tolerance, whereas those that failed did not [2,3].

JA2012 claimed that we [7] incorrectly conflated arguments about evolutionary potential and inbreeding depression. Yet Equation 1 predicts these are related in random mating populations, because inbreeding depression is causally related to \( F \) [2-4]. This theory applies here, because derivation of the \( N_e = 500 \) rule assumed neutral quantitative genetic variation [3,4]. Furthermore, the near-neutral theory of molecular evolution and genomic evidence indicates that populations of \( N_e = 500 \) are not immune to inbreeding depression, because fixed genetic loads still occur in populations with \( N_e > 500 \) [3]. For example, numbers of duplications and mobile elements, and larger introns (all usually deleterious) are negatively related to \( N_e \), over a range of approximately \( 10^4 - 10^6 \) [11]. Furthermore, the ratio of synonymous to nonsynonymous base changes (the latter resulting in altered amino acids) in humans (\( N_e \approx 10^4 \)) and murids (\( N_e \approx 10^6 \)) are 0.23 and 0.13, respectively, indicating differences in fixed genetic loads, even at \( N_e > 500 \) [12].

JA2012 commented: ‘A quick glance at the list of threatened species used [7]…indicates that their threat status was a result of the usual [human associated] agents of decline.’ However, Jamieson and Lacy [6] stated ‘We now recognize that genetic factors do not normally work in isolation, but instead often interact with factors that cause populations to decline in the first place…’, and [7] and others [2-4] made comparable statements.

Contradiction

The many assertions made by JA2012 (detailed above) about the lack of evidence for causal connections between genetic factors, population demography, and extinction risk contradict their statement that ‘Early doubt and controversy about whether genetic factors had any part to play in extinction risks of threatened organisms…have now mostly disappeared.’, because establishing the causal links between genetic factors and extinction risk were critical to resolving the controversy.

We are preparing an extended critique of JA2012 for another journal.

References

A school of red herring: reply to Frankham et al.

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In their Letter in TREE [1], Frankham et al. criticize several aspects of our review of how to apply the 50/500 rule to minimum viable populations (MVPs) [2]. Unfortunately, they do not address our primary conclusion, that the 500 in the 50/500 rule should not be used as a threshold to make triage decisions to allocate conservation resources. Neither do they address our assertion that converting 500 to a threshold of 5000 individuals using an \( N_e/N_c \) (effective over census population size) ratio of 10% is not appropriate because of the great variability in this ratio observed

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