FeO-containing K-Na-rich silicate ('KNSF': SiO_2 64.3 wt%, K_2O 18.6 wt%, Na_2O 12.4 wt%, FeO 4.6 wt%) with a low melting temperature. The experiments at the Australian National University (ANU) used $Pd_{90}Fe_{10}$ alloys made by melting mixes of Pd and Fe powders. These alloys were also fabricated into capsules and equilibrated with the FeO-containing K-Na-rich silicate. The silicate material was prepared from a mixture of reagent grade oxides and carbonates (K, Na), melted under air, and quenched to glass. Small cylinders were drilled out of the KNSF silicate glass and were inserted into capsules fabricated from the $Pd_{90}Fe_{10}$ and $Pt_{90}Fe_{10}$ alloys (BGI experiments). In the case of ANU experiments, silicate glass powders were loaded into the capsules. The metal phases of interest were used as capsule material to avoid contamination of the sample with capsule material in the metal–silicate partition experiments; for example, contamination by MgO or Al_2O_3 of silicate phases by using MgO- or Al_2O_3-capsules as shown in, for example, ref. 23. Graphite was used as the heater in piston-cylinder furnace assemblies and $LaCrO_3$ as the heater in multi-anvil furnaces. The entire assemblies were placed in a vacuum oven at 250 °C overnight before the experiment. Details of the experimental design and method can be found in refs 24 (piston cylinder) and 25 (multi-anvil). After reaching the desired pressure, samples were heated to the desired temperatures (1,100–1,600 °C). Experimental conditions were chosen so that solid metal and liquid silicate coexisted during the experiments. The low-melting KNSF-silicate remained above its liquidus within the investigated P–T-range. Run durations were up to 36 h, and the experiments were terminated by turning off the power to the heater. The temperature drop was sufficiently rapid to quench the silicate liquids into glasses. Metal compositions and major-element silicate compositions were determined by electron microprobe (Cameca Camebax, University of Cologne; 10 nA, 20 kV, counting time: 40 s). Palladium and Pt concentrations in silicates were analysed by an ultraviolet (quadrupled Nd-YAG) laser ablation-PlasmaQuad PQ-2+ inductively coupled plasma-mass spectrometer (ICP-MS) system at Memorial University, Newfoundland, Canada, using procedures described in ref. 26. The beam spot was 100 μm diameter, laser repetition rate 10 Hz, laser energy density 40 J cm^{-2}, and counting time 60 s. The Pd and Pt standards were homogeneous synthetic silicate glasses whose Pd and Pt concentrations had been measured previously by instrumental neutron activation analysis. The Si content of each individual silicate sample was used as an internal standard for the laser ablation ICP-MS analyses. To enhance the comparison between the high-pressure results and 1-atm data, additional 1-atm experiments with pure Pd and $Pt_{90}Fe_{10}$-metal and an FeO-containing melt ('BK': SiO_2 49.1 wt%, CaO 19.2 wt%, MgO 10.6 wt%, Al_2O_3 14.1 wt%, FeO 7.0 wt%) as silicate starting material were performed under controlled temperature and oxygen fugacity in gas mixing furnaces at the University of Cologne using the loop technique as described in ref. 27. The Pd and Pt contents in these silicate samples were analysed by instrumental neutron activation analysis at the University of Cologne.

Received 23 December 1999; accepted 6 June 2000.

1. Li, J. & Agee, C. B. Geochemistry of mantle-core differentiation at high pressure. *Nature* **381,** 686–689 (1996).
2. Righter, K. & Drake, M. J. Metal-silicate equilibrium in a homogeneously accreting Earth: new results for Re. *Earth Planet. Sci. Lett.* **146,** 541–553 (1997).
3. Borisov, A., Palme, H. & Spettel, B. Solubility of palladium in silicate melts: implications for core formation in the Earth. *Geochim. Cosmochim. Acta* **58,** 705–716 (1994).
4. Borisov, A. & Palme, H. Experimental determination of the solubility of platinum in silicate melts. *Geochim. Cosmochim. Acta* **61,** 4349–4357 (1997).
5. Ertel, W. *et al.* Solubilities of platinum and rhodium in a haplobasaltic melt at 1300°C. *Geochim. Cosmochim. Acta* **63,** 2439–2449 (1999).
6. Borisov, A. & Palme, H. The solubility of iridium in silicate melts: new data from experiments with $Ir_{10}Pt_{90}$ alloys. *Geochim. Cosmochim. Acta* **59,** 481–485 (1995).
7. Borisov, A. & Palme, H. Noble metal/silicate melt equilibria: experimental investigations and geochemical implications. *Eur. J. Mineral.* **9** (Suppl.), 59 (1997).
8. O'Neill, H. St C. *et al.* Experimental petrochemistry of some highly siderophile elements at high temperatures, and some implications for core formation and the mantle's early history. *Chem. Geol.* **120,** 255–273 (1995).
9. O'Neill, H. St C. & Palme, H. in *The Earth's Mantle, Composition, Structure and Evolution* (ed. Jackson, I.), 3–126 (Cambridge Univ. Press, Cambridge, 1998).
10. Murthy, V. R. Early differentiation of the Earth and the problem of mantle siderophile elements: a new approach. *Science* **253,** 303–306 (1991); corrections **253,** 1467 (1991).
11. Walter, M. Screws tighten on the core. *Nature* **398,** 563–565 (1999).
12. Ringwood, A. E. The Earth's core: its composition, formation and bearing upon the origin of the Earth. *Proc. R. Soc. Lond. A* **395,** 1–46 (1984).
13. Wänke, H., Dreibus, G. & Jagoutz, E. in *Archean Geochemistry* (ed. Kröner, A.) 1–24 (Springer, Berlin, 1984).
14. O'Neill, H. St C. The origin of the Moon and the early history of the Earth—a chemical model. Part 2: The Earth. *Geochim. Cosmochim. Acta* **55,** 1159–1172 (1991).
15. Walter, M. At the magma ocean floor. *Nature* **381,** 646–647 (1996).
16. Morgan, J. W., Wandless, G. A., Petrie, R. K. & Irving, A. J. Composition of the Earth's upper mantle-I. Siderophile trace elements in ultramafic nodules. *Tectonophysics* **75,** 47–67 (1981).
17. Jagoutz, E. *et al.* The abundances of major, minor and trace elements in the Earth's mantle as derived from primitive ultramafic nodules. *Proc. Lunar Planet. Sci. Conf.* **10,** 2031–2050 (1979).
18. Morgan, J. W. Ultramafic xenoliths: clues to Earth's late accretionary history. *J. Geophys. Res.* **91,** 12375–12387 (1986).
19. Kimura, K., Lewis, R. S. & Anders, E. Distribution of gold and rhenium between nickel-iron and silicate melts: implications for the abundances of siderophile elements on the Earth and Moon. *Geochim. Cosmochim. Acta* **38,** 683–701 (1974).
20. Holzheid, A., Palme, H. & Chakraborty, S. The activities of NiO, CoO and FeO in silicate melts. *Chem. Geol.* **139,** 21–38 (1997).
21. Hultgren, R., Desai, P. D., Hawkins, D. T., Gleiser, M. & Kelley, K. K. *Selected Values of the Thermodynamic Properties of Binary Alloys* (American Society for Metals, Metals Park, Ohio, 1973).
22. Meisel, T., Walker, R. J. & Morgan, J. W. The osmium isotopic composition of the Earth's primitive upper mantle. *Nature* **383,** 517–520 (1996).
23. Hillgren, V. J., Drake, M. J. & Rubie, D. C. High-pressure and high-temperature experiments on core-mantle segregation in the accreting Earth. *Science* **264,** 1442–1445 (1994).
24. Seckendorff, V. & O'Neill, H. St C. An experimental study of Fe-Mg partitioning between olivine and orthopyroxene at 1173, 1273, and 1423 K and 1.6 GPa. *Contrib. Mineral. Petrol.* **113,** 196–207 (1993).
25. Rubie, D. C., Karato, S., Yan, H. & O'Neill, H. St C. Low differential stress and controlled chemical environment in multi-anvil high pressure experiments. *Phys. Chem. Miner.* **20,** 315–322 (1993).
26. Sylvester, P. J. & Eggins, S. M. Analysis of Re, Au, Pt, Pd, and Rh in NIST glass certified reference materials and natural basalt glasses by laser ablation-ICP-MS. *Geostand. Newsl.* **21,** 215–229 (1997).
27. Holzheid, A. & Palme, H. The influence of FeO on the solubilities of Co and Ni in silicate melts. *Geochim. Cosmochim. Acta* **60,** 1181–1193 (1996).

Acknowledgements

High pressure experiments were performed at the Bayerisches Geoinstitut under the EU 'TMR - Large Scale Facilities' (D.C.R.) programme.

Correspondence should be addressed to A.H. (e-mail: holzheid@uni-muenster.de).

Mutation and sex in a competitive world

Joel R. Peck & David Waxman

Centre for the Study of Evolution, The University of Sussex, Brighton BN1 9QG, UK

How do deleterious mutations interact to affect fitness? The answer to this question has substantial implications for a variety of important problems in population biology, including the evolution of sex[1–3], the rate of adaptation[4,5] and the conservation of small populations[3,6–8]. Here we analyse a mathematical model of competition for food in which deleterious mutations affect competitive ability. We show that, if individuals usually compete in small groups, then competition can easily lead to a type of genetic interaction known as synergistic epistasis. This means that a deleterious mutation is most damaging in a genome that already has many other deleterious mutations. We also show that competition in small groups can produce a large advantage for sexual populations, both in mean fitness and in ability to resist invasion by asexual lineages. One implication of our findings is that experimental efforts to demonstrate synergistic epistasis may not succeed unless the experiments are redesigned to make them much more naturalistic.

Consider a population of organisms for which generations are discrete, so that parents die at around the time that their offspring are produced. Let us define an adult as an individual that survives to reproductive age. We define the fitness associated with a particular genotype as the mean number of surviving offspring produced by adults with that genotype. In other words, when calculating fitness, we only count offspring that survive to adulthood.

Let us suppose that the fitness associated with a genotype depends only on the number of deleterious mutations. It is useful to normalize fitness, so we define a quantity, w_k, which is the fitness associated with having k deleterious mutations divided by the fitness associated with having zero deleterious mutations (thus, $w_0 = 1$). That is, w_k is the relative fitness of adults with k mutations.

If mutations act entirely independently of each other, then a plot of the logarithm of w_k as a function of k (the number of mutations) produces a straight line with a negative slope. This is the case where epistasis is absent, and mutations combine to affect fitness in a multiplicative fashion. If each mutation added to the genome has a greater deleterious effect than preceding mutations, then we have synergistic epistasis, leading to a curve where the rate of decrease in the logarithm of w_k increases with k (Fig. 1a). If each mutation

added to the genome has a smaller deleterious effect on fitness than preceding mutations, then we have diminishing returns epistasis, where the rate of decrease in the logarithm of w_k declines with k (Fig. 1b).

Let $\bar{w}$ represent the mean value of w_k at equilibrium (that is, $\bar{w}$ is the mean relative fitness). Analysis of simple models shows that, in the case of no epistasis, we have $\bar{w} = e^{-U}$, where U is the expected number of new mutations per offspring[1,9]. For diminishing-returns epistasis these models yield $\bar{w} < e^{-U}$, and for synergistic epistasis, $\bar{w} > e^{-U}$.

The theoretical findings have focused the attention of experimentalists on synergistic epistasis[1,10–16]. However, there is no strong experimental support for the idea that synergistic epistasis is ubiquitous[13,16]. This is surprising because, in the absence of synergistic epistasis, it is difficult to explain how species with relatively small local populations (for example, mammals and trees) can survive genetic drift[3,7]. Populations with high genomic mutation rates (U) are also difficult to explain without synergy, and there is evidence that high values of U may be common[3,17–21].

The present state of nature is puzzling, given the lack of success in demonstrating synergistic epistasis. We believe that the explanation is that synergy emerges in nature primarily from competition for resources among small groups of genetically diverse individuals. This type of situation is common, but it is more complex than what has been considered in most of the experimental work on synergy[1,10–16]. Several authors have speculated that synergy emerges from competition for resources[22,23]. However, as we shall see, there is no general reason to expect competition for resources to lead to synergy unless competition generally takes place in small groups. The authors who have gone furthest to emphasize the importance of competition in small groups as a source of synergy are A. S. Kondrashov[1] and W. D. Hamilton *et al.*[24], but they discussed small-group competition very briefly and without analysis of a formal model.

To understand the importance of competition, let us consider a simple model. We will focus on one specific case, but we believe that analysis of this case provides general insight.

Consider a diploid and outcrossing organism that depends on consuming a resource called 'food'. Generations are discrete, and the expected number of offspring for a female adult is proportional to the amount of food she eats between reproductive maturity and death. Offspring are male or female, with equal probability. For convenience, we measure food in units such that the expected number of offspring increases by one for each unit of food consumed. We also make the convenient assumption that food appears in discrete quantities (these might be seeds, fruits or individual prey animals).

Each offspring is produced by a female adult after mating with a male adult, and the probability that a male adult will contribute to a particular offspring is assumed to be proportional to the amount of food that the male has consumed since maturation. This may reflect a better ability to compete for mates among better-fed males. Alternatively, for a 'broadcast breeder', this may reflect proportionality between the amount of food consumed and the number of male gametes produced.

Standard mendelian segregation and free recombination are involved in the production of gametes. A very large number of loci are susceptible to deleterious mutations. During gamete production, mutations occur independently at randomly selected loci, and the expected number of new mutations per gamete is $U/2$. Thus, the expected number of new mutations per offspring is U.

We assume that an adult's genetic constitution controls the rate at which it can consume food. An adult with k mutations can consume food at a rate of C_k (where $C_k > 0$). The mutations are deleterious, and thus we assume that $C_{k+1}/C_k \leq (1 - \epsilon)$, for some ϵ that satisfies $0 < \epsilon < 1$. Note that these assumptions are fairly general in that many different relationships between the number of mutations and competitive ability are allowed within the model.

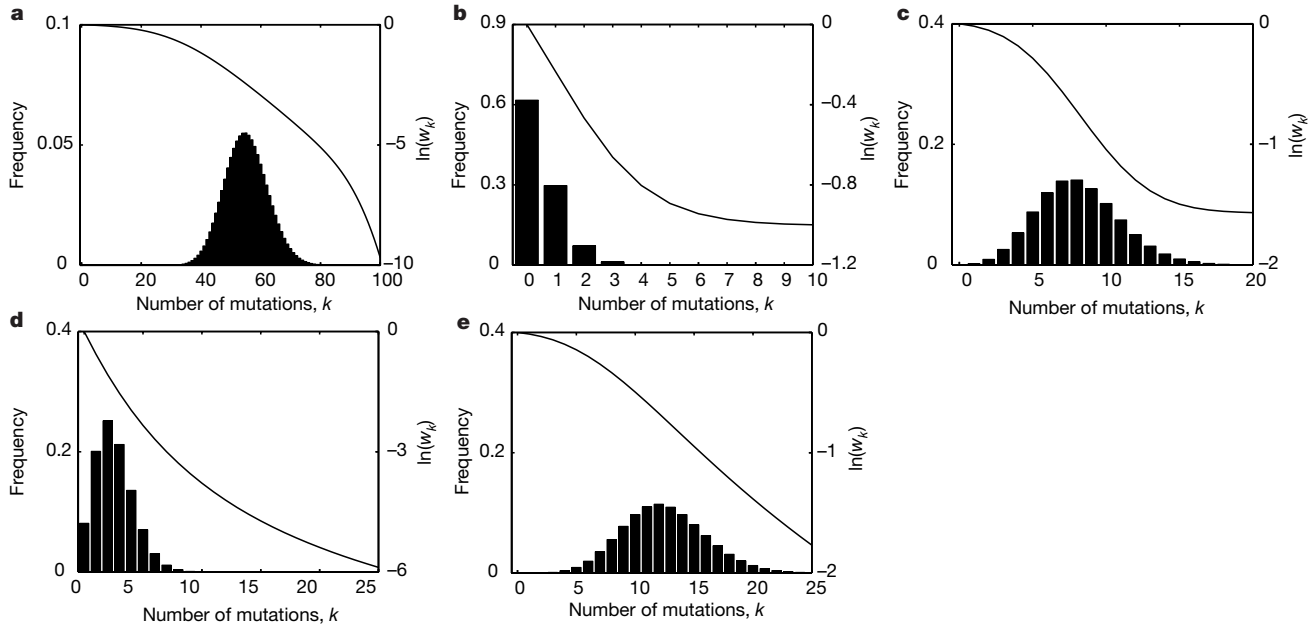

Figure 1 Results of five numerical studies. In each case, the histogram gives the equilibrium frequencies of adults with k mutations, where $k = 0, 1, 2, 3, \ldots$ The curve gives the natural logarithm of the w_k values. The value of w_k is the expected number of offspring for an adult with k deleterious mutations divided by the expected number of offspring for an adult with no deleterious mutations (measured at equilibrium). The parameter values used are: **a**, $\alpha = 0.2$, $\Theta = 100$, $\gamma = 0.01$, $U = 4.5$, $C_k = 0.9^k$; **b**, $\alpha = 0.04$, $\Theta = 100$, $\gamma = 10^{-9}$, $U = 0.1$, $C_k = 0.5^k$; **c**, $\alpha = 0.04$, $\Theta = 100$, $\gamma = 10^{-9}$, $U = 1.0$, $C_k = 0.5^k$; **d**, $\alpha = 0.04$, $\Theta = 2,000$, $\gamma = 0.01$, $U = 1.0$, $C_0 = 1$, $C_k = \Pi_{i=1}^{k}[0.95 - 0.4e^{-0.1(i-1)}]$ for $k \geq 1$; **e**, $\alpha = 0.04$, $\Theta = 100$, $\gamma = 0.01$, $U = 1.0$, $C_0 = 1$, $C_k = \Pi_{i=1}^{k}[0.95 - 0.4e^{-0.1(i-1)}]$ for $k \geq 1$. At equilibrium, the values of $\bar{n}$ (the mean number of adults consuming a food item), $\bar{k}$ (the mean number of mutations per adult) and $\bar{w}$ (the mean of w_k) are: **a**, $\bar{n} = 6.98$, $\bar{k} = 55.057$, $\bar{w} = 0.104$; **b**, $\bar{n} = 1.594$, $\bar{k} = 0.483$, $\bar{w} = 0.904$; **c**, $\bar{n} = 1.594$, $\bar{k} = 8.117$, $\bar{w} = 0.512$; **d**, $\bar{n} = 39.973$, $\bar{k} = 2.549$, $\bar{w} = 0.355$; **e**, $\bar{n} = 0.400$, $\bar{k} = 12.446$, $\bar{w} = 0.508$.

Members of our hypothetical population spend their time looking for and consuming food items. Once an adult encounters and begins to consume a food item, consumption continues until the food item is gone. The quantity of food in a food item decreases as a result of both consumption and decay. Decay occurs at rate γ (where $\gamma > 0$). For convenience, we assume that, when consumption begins, all food items contain α units of food. Thus, if n adults consume a food item at the same time, and they have a mean rate of consumption $\overline{C}$, then the food item will disappear after $\alpha/(n\overline{C} + \gamma)$ time units (where $n \geq 1$). In this case, the amount of a food item that is consumed by an adult with k mutations is $\alpha C_k/(n\overline{C} + \gamma)$.

Let Θ denote the expected value for the number of food items that an adult will encounter between maturation and death. We assume that variation among adults in the value of Θ is negligible, and so treat Θ as a constant. This suggests that adults spend a negligible amount of their time consuming food, compared to the amount of time spent looking for food.

The number of adults that consume each food item is assumed to follow a Poisson distribution with mean $\bar{n}$. Thus, a proportion $\exp(-\bar{n})$ of food items are never consumed. The individuals that

Box 1

The main mathematical details of the analysis

The population is assumed to be sufficiently large that stochastic effects may be ignored. In one particular generation, p_k denotes the frequency of adults with k mutations. Quantities associated with the following generation are indicated by a prime. Results are presented here only for the sexual population (results for the asexual population follow straightforwardly).

We census adults immediately before the production of gametes. The expected number of offspring produced by a female with k mutations is F_k.

The rule connecting $\bar{n}$ in adjacent generations is $\bar{n}' = \bar{n}\bar{F}/2$, where $\bar{F} = \Sigma_{k=0}^{\infty} F_k p_k$. Thus at equilibrium, when $\bar{n}' = \bar{n}$, the expected number of offspring is two for every female.

No runaway theorem for $\bar{k}$

We shall establish here the result that for the sexual population, the mean number of mutations, $\bar{k} = \Sigma_{k=0}^{\infty} k p_k$, cannot increase indefinitely. Thus if, in one generation, $\bar{k}$ is sufficiently large, then for the following generation, $\bar{k}' < \bar{k}$.

It follows from the dynamical equation relating p_k in adjacent generations that

$$\bar{k}' = U + \sum_{k=0}^{\infty} k F_k p_k \Big/ \bar{F} \tag{2}$$

Let us first analyse this equation when $\gamma = 0$. Although this value of γ is not allowed within the model, it will provide useful information for the allowed case: $\gamma > 0$.

For $\gamma = 0$, it can be shown that $\bar{F} = \alpha\Theta[1 - \exp(-\bar{n})]/\bar{n}$, and equation (2) can be written as

$$\bar{k}' - \bar{k} = U + \frac{\alpha\Theta}{\bar{F}} \sum_{m=0}^{\infty} \frac{Q(m)}{m+1} \sum_{k_0 k_1 \ldots k_m} \left(\frac{\Sigma_{j=0}^{m} k_j C(k_j)}{\Sigma_{j=0}^{m} C(k_j)} - \frac{\Sigma_{j=0}^{m} k_j}{\Sigma_{j=0}^{m} 1} \right) p_{k_0} p_{k_1} \ldots p_{k_m} \tag{3}$$

where $Q(m) = \bar{n}^m \exp(-\bar{n})/m!$. For all m, the expression on the right-hand side of equation (3) inside brackets is negative (using Chebyshev's inequality: see equation (11.115) of ref. 30). Furthermore, the leading non-zero term in the sum over m on the right-hand side of equation (3) occurs at $m = 1$. This is the contribution from two adults encountering and consuming a food item. Assuming that the mean number of adults per food item, $\bar{n}$, is finite, it follows that $Q(1)$ is finite and a non-negligible proportion of food items are encountered by two adults. We shall show that when $\bar{k}$ is sufficiently large in one generation, the contribution from just the $m = 1$ term on the right-hand side of equation (3) is sufficiently negative that $\bar{k}'$ will be smaller than $\bar{k}$. As a consequence, the mean number of mutations cannot increase indefinitely with time in a sexual population.

We separate the possible distributions of mutations among adults into two cases that cover all possibilities.

Case (1). The proportion of all adults, in one generation with $< \bar{k}/4$ mutations is $\leq \lambda$ (where $\lambda \neq 0, 1$).

In the next generation, in which $\bar{k}$ is calculated, a proportion $\geq (1 - \lambda)^4$ of the food items consumed by two adults will be eaten by individuals whose parents both had $\geq \bar{k}/4$ mutations.

The gametes produced by two parents with a large number of mutations will be normally distributed with a mean of one-half the parental number of mutations and a variance of one-quarter the parental number of mutations. Thus the mean number of mutations in offspring produced from two parents with $\geq \bar{k}/4$ mutations is $\geq \bar{k}/4$ and the variance in the number of mutations in these offspring is $\geq \bar{k}/8$.

The contribution to $\bar{k}' - \bar{k}$ from the $m = 1$ term of equation (3) can be written

$$-\frac{\alpha\Theta Q(1)}{4\bar{F}} \sum_{k_0 k_1} |k_1 - k_0| \frac{|C(k_1) - C(k_0)|}{C(k_1) + C(k_0)} p_{k_0} p_{k_1} \tag{4}$$

The contribution to this from the offspring of two parents with $\geq \bar{k}/4$ mutations is of order $-\alpha\Theta Q(1)(1 - \lambda)^4 \sqrt{\bar{k}}/\bar{F}$ (more refined estimates can be made, but the result given is adequate for our purposes). Thus for sufficiently large $\bar{k}$, this contribution becomes large and negative and forces $\bar{k}' - \bar{k}$ to be negative, thereby preventing runaway of the mean number of mutations.

Case (2). The proportion of all adults, in one generation, with $< \bar{k}/4$ mutations is $> \lambda$ (where $\lambda \neq 0, 1$).

In this case, some adults have $< \bar{k}$ mutations and there must be other adults with $> \bar{k}$ mutations. Let the proportion of the adults with $> \bar{k}$ mutations be R. We focus on food items that are consumed by exactly two adults where both parents of one adult had $< \bar{k}/4$ mutations and the other adult had at least one parent with $> \bar{k}$ mutations. Under the current assumptions, the frequency with which consumed food items fall into this category is at least $2R(1 - R)\lambda^2$. Furthermore, when $\bar{k}$ is very large, the difference in the number of mutations of adults on all but a negligible proportion of such food items must be at least of the order of $\bar{k}$. As a consequence, the contribution to $\bar{k}' - \bar{k}$ arising from such food items is, from equation (4), of order $-\alpha\Theta Q(1)R(1 - R)\lambda^2 \sqrt{\bar{k}}/\bar{F}$. For sufficiently large $\bar{k}$, this contribution becomes large and negative and forces $\bar{k}' - \bar{k}$ to be negative.

Cases (1) and (2) indicate that for $\gamma = 0$, $\bar{k}$ does not $\rightarrow \infty$. Provided all consumers of a food item have a finite number of mutations, the behaviour in γ is continuous as $\gamma \rightarrow 0$. Thus for $\gamma \rightarrow 0$ the $\gamma = 0$ results are obtained.

Other results

A number of other results are contained in the main text. Here we provide details of their derivation.

The equilibrium value of $\bar{n}$ for $\gamma \rightarrow 0$, is given by the positive solution of $2\bar{n} = \alpha\Theta[1 - \exp(-\bar{n})]$. This follows when $\bar{F} = \alpha\Theta[1 - \exp(-\bar{n})]/\bar{n}$ (which applies for $\gamma \rightarrow 0$), is used in the update rule for $\bar{n}$ at equilibrium: $\bar{n}' = \bar{n}\bar{F}/2$.

The condition for invasion of a sexual population by asexuals follows by first noting the number of offspring produced by a mutation-free asexual invader. This number is identical to that of a mutation free sexual, namely F_0, because the asexual is in competition only with sexuals for food. The critical mutation rate U_1^* is that for which a mutation-free asexual is just able to replace itself with another mutation free individual, given by $\exp(-U_1^*)F_0 = 1$. As $\bar{w} = \bar{F}/F_0$ and at equilibrium $\bar{F} = 2$, it follows that U_1^* is determined by $\exp(-U_1^*)(2/\bar{w}) = 1$, which is equivalent to the expression given in the main text.

In the modified model, where there is a maximum value of $\bar{n}$, namely $\bar{n}_{\max}$, we note that $F_0 < \alpha\Theta$ and individuals are expected to encounter at least $\Theta \exp(-\bar{n}_{\max})$ food items that are not encountered by any other individual. Thus $\bar{F} > \alpha\Theta \exp(-\bar{n}_{\max})$, so $\bar{w} > \exp(-\bar{n}_{max})$, and we have the bound $U_1^* < \bar{n}_{\max} + \ln(2)$.

consume a particular food item are a random sample of the adults, and we take $\bar{n}$ to be proportional to the number of adults in the population (which is assumed to be very large). In our numerical studies we initially take $\bar{n} = \alpha\Theta$, and initially all adults have no mutations.

Extensive numerical study suggests that this model always leads to equilibrium. We determine the w_k values only after equilibrium is reached.

Consider the case where, at equilibrium, the mean number of individuals per food item ($\bar{n}$) is very large ($\bar{n} \to \infty$). In this case, we can show that w_k is proportional to C_k for all $k \geq 0$. Thus, when $\bar{n}$ is very large, there is no a priori reason to expect synergistic epistasis to emerge from competition for resources.

A very large value of $\bar{n}$ can only be achieved if the availability of food ($\alpha\Theta$) is also very large. When food availability is more limited a variety of patterns are possible (Fig. 1). Figure 1a–c uses multiplicative C_k functions. This sort of function leads to the logarithm of w_k declining linearly with k when $\bar{n}$ is very large. However, when food availability is limited, multiplicative C_k functions can lead to synergistic epistasis (Fig. 1a), diminishing-returns epistasis (Fig. 1b) or a combination of the two (Fig. 1c).

Despite the variety of patterns that arise when food availability is limited, it is possible to say something general in the case where γ (the rate of food decay) is very small ($\gamma \to 0$). In this case, we can show that for k sufficiently large (but finite) we have $w_{k+1}/w_k \approx 1$. In other words, if we consider individuals with sufficiently large numbers of mutations, then any additional mutations have a negligible effect on fitness. We can expect the effect of additional mutations on fitness to be non-negligible for some smaller values of k. Thus, when γ is very small, we will have diminishing-returns epistasis for sufficiently large values of k (Fig. 1b, c). These findings arise because adults with many more mutations than average will consume almost no food from food items that are consumed by multiple adults (because these food items will be consumed very quickly, relative to the rate of consumption for such adults). However, if γ is very small, these mutation-laden adults will consume almost all of any food items that they alone encounter.

Another case where it is possible to say something general about the shape of the w_k curve is where γ is very small ($\gamma \to 0$), $\bar{n}$ is not very large and nearly all members of the population have such large numbers of mutations that they consume food items very slowly in comparison with individuals with few mutations. In this case, adults with only a few deleterious mutations will generally consume food items very quickly in comparison with the rate of food decay, and in comparison with any other adults that are consuming the same food item. Therefore, these adults will usually consume nearly all of any food item they encounter. Thus, $w_{k+1}/w_k \approx 1$ for sufficiently small values of k. For values of k closer to the mean we can expect smaller values of w_{k+1}/w_k because of competition with other adults. Thus, regardless of the details of the pattern of C_k values, synergistic epistasis can be expected for sufficiently small values of k (Fig. 1a, c, e).

This mechanism for producing synergy requires a sufficiently small value of $\bar{n}$, and so food availability ($\alpha\Theta$) must be sufficiently small. With this in mind, consider Fig. 1d and e which uses a function for C_k that gives diminishing-returns epistasis when food availability is sufficiently large. For Fig. 1d we set $\Theta = 2{,}000$, leading to an equilibrium where $\bar{n} = 39.973$. As a consequence of this substantial $\bar{n}$ value, the w_k values shown are similar to the C_k values (all are within 8%), and diminishing-returns epistasis prevails. When food availability is cut to $\Theta = 100$, $\bar{n} = 0.400$ at equilibrium. As a consequence, the w_k values show synergistic epistasis (Fig. 1e).

Another possible source of synergistic epistasis relates to food decay. In a sense, adults must compete against food decay in a way that is similar to the competition they experience with each other. However, this source of synergy is unimportant when γ is low relative to the average rate of food consumption. This is easily demonstrated. For example, decreasing the value of γ from 0.01 to 10^{-9} does not cause much change in the w_k values in Fig. 1a (data not shown).

The population described above will survive only if females consume enough food to produce at least two offspring each (on average). In the limit as $\gamma \to 0$ the condition for survival of a sexual population is $\alpha\Theta > 2$. This means that, when $\alpha\Theta > 2$, a sexual population can survive any finite rate of mutation (U) so long as γ is sufficiently small. (Proofs are given in Box 1). We also find that when $\alpha\Theta > 2$ and we take the limit as $\gamma \to 0$, the equilibrium population density takes on a value such that the equilibrium value of $\bar{n}$ is given by the positive solution of $2\bar{n} = \alpha\Theta[1 - \exp(-\bar{n})]$. Note that, in this case, U has no influence on the equilibrium population density. These results arise because, when γ is very small, population extinction cannot occur unless the mean number of mutations per adult ($\bar{k}$) is very large, so that the average rate of food consumption is depressed at least to the point where food consumption occurs at a similar rate to food decay (γ). A low γ and a high $\bar{k}$ are exactly the conditions specified above for the emergence of synergistic epistasis over sufficiently small values of k. Furthermore, these conditions tend to produce situations where $w_k \approx 1$ for all but very large values of k. Functions of this sort are known to be particularly beneficial for sexual populations[1].

Next, consider the limit as $U \to 0$. In this limit, the condition for survival of a sexual population is $\alpha\Theta > 2(1 + \gamma/C_0)$.

What happens to a sexual population when $U \gg 0$ and $\gamma \gg 0$? The answer depends on the exact choice of parameter values. However, so long as $\alpha\Theta > 2$ it is not difficult to find parameter values for which a sexual population can survive, but an asexual population (described below) will go extinct. This can be done by choosing γ sufficiently small and U sufficiently large (see Fig. 2 for examples).

Let us consider an asexual population that is identical to the one just described except that all individuals are female, and each offspring is genetically identical to its parent, except for new mutations. Mutations occur at the same rate per locus as in the

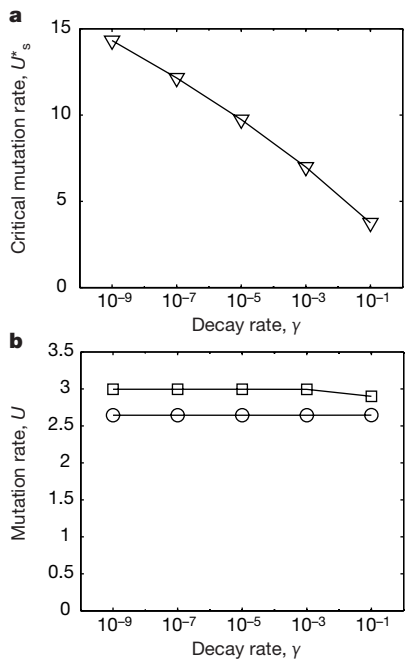

Figure 2 Results from the numerical studies. **a**, The values of U^*_S, the genomic mutation rate above which a sexual population goes extinct. **b**, Squares, values of U^*_A, the genomic mutation rate above rate above which an asexual population will go extinct. Circles, values of U^*_I, the genomic mutation rate above which a sexual population at equilibrium cannot be successfully invaded by an asexual lineage. For all data shown, $\alpha = 0.2$, $\Theta = 100$, $C_k = 0.9^k$.

sexual population described above, and thus the mean number of new mutations per genome is U.

This asexual population will perpetuate itself indefinitely so long as the average amount of food consumed per adult is sufficient to produce at least one offspring. This is half the food requirements of a sexual population, which reflects the well known two-fold cost of sex[25]. Over the long term, the rate of food consumption can be maintained at a sufficiently high level only if

$$\frac{\alpha\Theta e^{-U}}{1+\gamma/C_0} \geq 1 \qquad (1)$$

If this relation is not satisfied, the population will go extinct. This result is in sharp contrast to the situation in sexuals. Whenever $e^U > \alpha\Theta > 2$ and γ is sufficiently small, we have a situation where a sexual population can survive but an asexual population will go extinct (for any allowable values of C_k). For example, if γ is very small, then this is the case when $\alpha\Theta = 2.5$ and $U > 0.917$, and also when $\alpha\Theta = 25$ and $U > 3.22$.

Let us consider the conditions required for a sexual population to be safe from invasions into its habitat by asexual populations that consume the same food. The results will also tell us when a sexual population is safe from mutations that cause asexual reproduction and eliminate the 'cost of sex' by causing female adults to produce only female offspring. Mutations (or sets of mutations) of this sort seem to be responsible for the origination of many asexual populations[26–28].

Suppose that the invading asexuals are as described above, and have the same mutation rate and C_k values as the sexuals. We assume that the asexuals are initially very rare, so that they compete with sexuals for food, but they rarely compete with each other for the same food item. Under these conditions, we find that a sexual population at equilibrium cannot be invaded by asexuals so long as the genomic mutation rate (U) is sufficiently large. Let U_I^* represent the value of U above which asexuals can never invade by increasing from a very low initial density (I is for invasion). If $U < U_I^*$ then invading asexuals may increase to a non-negligible density (such an increase is guaranteed if $U < U_I^*$ and many of the asexual invaders are free of deleterious mutations). It can be shown that $U_I^* = \ln(2/\bar{w})$, where $\bar{w}$ is the mean value of w_k. The values of w_k and $\bar{w}$ can be derived from numerical study of a sexual population (see Fig. 2 for an example). We can also show that, in all cases, $U_I^* \leq \ln(\alpha\Theta)$.

In our model, food availability has a strong effect on population density. In many natural populations, however, population density is largely determined by other factors, such as predation and parasitism[29]. We can modify the model to emulate these processes in a very rough way by assuming that the mean number of adults per food item ($\bar{n}$) can never exceed a particular value, denoted $\bar{n}_{max}$. Assume that, if the population at birth is such that the number of newborn individuals per food item is greater than $\bar{n}_{max}$, then a 'thinning' process takes place so that randomly selected newborns die until $\bar{n} = \bar{n}_{max}$.

If $\bar{n}_{max}$ is sufficiently large then thinning never occurs. What happens, however, if $\bar{n}_{max}$ is small enough so that thinning does occur? The condition for survival of an asexual population is unaffected, and is still given by relation (1). Furthermore, a sexual population can still survive so long as $\alpha\Theta > 2$ and γ is sufficiently small. Perhaps the most intriguing effect is the impact on U_I^*. For any choice of parameter values such that $\alpha\Theta > 2$, we have, in the limit as $\gamma \to 0$, $U_I^* < [\bar{n}_{max} + \ln(2)]$. Thus, if γ is sufficiently small, we can bring U_I^* arbitrarily close to $\ln(2) = 0.693$ by decreasing the value of $\bar{n}_{max}$. This is because when γ is sufficiently small and $\bar{n}_{max}$ is also small, competitions over food items are rare, and so the fitness of mutation-free individuals is not much higher than the mean fitness. This limits the maximum possible advantage of mutation-free asexual invaders.

Figure 3 shows data for a set of numerical studies that used the same parameter values used for Fig. 2, except that $\bar{n} = 1.386$, so that 25% of the food items that adults consume are consumed by no other adult. Comparison of Fig. 2 with Fig. 3 shows that the imposition of a maximum population density causes a substantial decrease in U_I^* in this case. With the preceding analytic result, this suggests that, when γ is sufficiently small, sexual populations will tend to be best protected from invasions by asexuals when their population density is kept low enough to allow many food items to be consumed by only one adult.

Our results show that synergistic epistasis can emerge from competition for food. Similar models can be constructed to show that synergy can arise from competition for other limited resources such as nest sites, places in which to shelter, distance from predators, access to light (in plants) and so on. In sexual organisms, the interactions involved in competing for mates may be a particularly important cause of synergistic epistasis. Additionally, deleterious mutations are just one source of variation in fitness. It is reasonable to expect results similar to those produced here for other sources of variation (for example, environmental change or spatial heterogeneity and migration).

To our knowledge, there has never been an experimental search for synergy that has allowed members of a genetically diverse population to compete in many randomly formed groups. Our results indicate that without such an approach, there may never be a convincing demonstration of the reality of synergistic epistasis. Our results also suggest that experimenters should be cautious, because, as shown in Fig. 1, synergistic epistasis may not hold over the entire range of mutation-contamination levels observed within a population. □

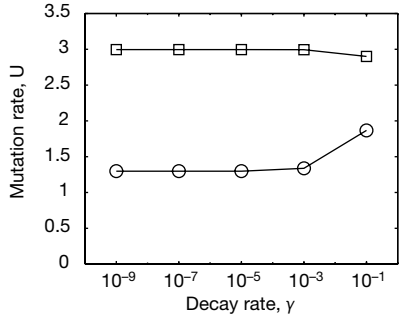

Figure 3 Results from the numerical studies using the modified model, for which there is a maximum allowable value of $\bar{n}$. Squares, values of U_A^*, the genomic mutation rate above which an asexual population will go extinct. Circles, values of U_I^*, the genomic mutation rate above which a sexual population at equilibrium cannot be successfully invaded by an asexual lineage. The U_S^* values are identical to those shown in Fig. 2. For all data shown, $\bar{n}_{max} = 1.386$, $\alpha = 0.2$, $\Theta = 100$, $C_k = 0.9^k$.

Received 11 January; accepted 9 May 2000.

1. Kondrashov, A. S. Deleterious mutations and the evolution of sexual reproduction. *Nature* **336,** 435–440 (1988).
2. Charlesworth, B. Mutation-selection balance and the evolutionary advantage of sex and recombination. *Genet. Res.* **55,** 199–221 (1990).
3. Peck, J. R., Barreau, G. & Health, S. C. Imperfect genes, Fisherian mutation and the evolution of sex. *Genetics* **145,** 1171–1199 (1997).
4. Charlesworth, B. Directional selection and the evolution of sex and recombination. *Genet. Res.* **61,** 205–224 (1993).
5. Waxman, D. & Peck, J. R. Sex and adaptation in a changing environment. *Genetics* **153,** 1041–1053 (1999).
6. Kondrashov, A. S. Muller's ratchet under epistatic selection. *Genetics* **136,** 1469–1473 (1994).
7. Kondrashov, A. S. Contamination of the genome by very slightly deleterious mutations—why have we not died 100 times over? *J. Theor. Biol.* **175,** 583–594 (1995).
8. Butcher, D. Muller's ratchet, epistasis and mutation effects. *Genetics* **141,** 431–437 (1995).
9. Kimura, M. & Maruyama, T. The mutational load with epistatic gene interactions in fitness. *Genetics* **54,** 1337–1351 (1966).
10. Crow, J. F. in *Mathematical Topics in Population Genetics* (ed. Kojima, K.) (Springer, Berlin, 1970).
11. de Visser, J. A. G. M., Hoekstra, R. F. & van den Ende, H. An experimental test for synergistic epistasis and its application in *Chlamydomonas*. *Genetics* **145,** 815–819 (1997).
12. de Visser, J. A. G. M. & Hoekstra, R. F. Synergistic epistasis between loci affecting fitness: evidence in plants and fungi. *Genet. Res.* **71,** 39–49 (1998).

13. Elena, S. F. & Lenski, R. E. Test of synergistic interactions among deleterious mutations in bacteria. *Nature* **390,** 395–398 (1997).
14. Koelewijn, H. P. Effects of different levels of inbreeding on progeny fitness in *Plantago coronopus*. *Evolution* **52,** 692–702 (1998).
15. West, S. A., Peters, A. D. & Barton, N. H. Testing for epistasis between deleterious mutations. *Genetics* **149,** 435–444 (1998).
16. Willis, J. H. Effects of different levels of inbreeding on fitness components in *Mumulus Guttaltus*. *Evolution* **47,** 864–876 (1993).
17. Eyre-Walker, A. & Keightley, P. D. High genomic deleterious mutation rates in hominids. *Nature* **397,** 344–347 (1999).
18. Eyre-Walker, A. Evidence of selection on silent site base composition in mammals: Potential implications for the evolution of isochores and junk DNA. *Genetics* **152,** 675–683 (1999).
19. Fry, J. D., Keightley, P. D., Heinsohn, S. L. & Nuzhdin, S. V. New estimates of the rates and effects of mildly deleterious mutation in Drosophila melanogaster. *Proc. Natl Acad. Sci. USA* **96,** 574–579 (1999).
20. Kondrashov, A. S. & Turelli, M. Deleterious mutations, apparent stabilizing selection and the maintenance of quantitative variation. *Genetics* **132,** 603–618 (1992).
21. Peck, J. R. & Eyre-Walker, A. The muddle about mutations. *Nature* **387,** 135–136 (1997).
22. Sved, J. A., Reed, T. E. & Bodmer, W. F. The number of balanced polymorphisms that can be maintained in a natural population. *Genetics* **55,** 469–481 (1967).
23. King, J. L. Continuously distributed factors affecting fitness. *Genetics* **55,** 483–492 (1967).
24. Hamilton, W. D., Axelrod, R. & Tanese, R. Sexual reproduction as an adaptation to resist parasites (a review). *Proc. Natl Acad. Sci. USA* **87,** 3566–3573 (1990).
25. Maynard Smith, J. *The Evolution of Sex* (Cambridge Univ. Press, Cambridge, 1978).
26. Parker, E. D. in *Evolutionary Genetics from Molecules to Morphology* (eds Singh, R. & Krimbas, C.) 450–475 (Cambridge Univ. Press, Cambridge, 2000.
27. Nygren, A. Apomixis in the angiosperms. *Bot. Rev.* **20,** 577–649 (1954).
28. Bell, G. *The Masterpiece of Nature* (Univ. California Press, San Francisco, 1982).
29. Krebs, C. J. *Ecology* 4th edn (Harper Collins, New York, 1994).
30. Gradshteyn, I. S. & Ryzhik, I. M. *Table of Integrals, Series and Products* (Academic, New York, 1980).

Acknowledgements

We thank J. Crow, A. Eyre-Walker, A. Kondrashov and J. Maynard Smith for advice. This study was supported by the Biotechnology and Biological Sciences Research Council (UK).

Correspondence and requests for materials should be addressed to J.R.P. (e-mail: j.r.peck@sussex.ac.uk).

Long-term vocal recognition in the northern fur seal

Stephen J. Insley

Animal Behavior Group, University of California, Davis, California 95616 and Department of Zoological Research, National Zoological Park, Smithsonian Institution, Washington DC 20008, USA

The ability to recognize and remember individual identities for long periods of time has important implications for the evolution of animal social behaviour, particularly complex interactions such as cooperation or mate choice[1–7]. Despite this importance, there is only a single example of long-term individual recognition in nature, the 8-month retention of neighbour's song among male hooded warblers, *Wilsonia citrina*[7], and there is none for a non-human mammal. Associations between individuals spanning years, which are especially prevalent in carnivores[8], primates[9] and seabirds[10], and evidence of mate fidelity[11,12] provide indirect support for the ability of long-term recognition. In many of these instances, however, individuals do not separate for extended periods, and thus long-term recognition, although often assumed, may be both unnecessary and nonexistent. Furthermore, site fidelity rather than individual recognition may explain many instances of mate fidelity[10]. Here I show that mother–offspring pairs of a migratory otariid pinniped—the northern fur seal (*Callorhinus ursinus*)—not only have the ability to recognize each other's vocalizations during the course of a breeding season, but are also able to retain these memories for at least 4 years.

Vocal recognition is a key component of offspring survival among northern fur seal maternal dyads and consequently both mothers and pups are very responsive to vocal playback studies[13,14]. Throughout nursing, mothers leave on week-long foraging trips and upon their return must relocate their pups in dense breeding colonies using what appears to be a combination of geographic, vocal and olfactory cues. At four months of age, pups migrate south independent of their mothers[15,16]. The seals spend winter at sea, travelling as far south as the Channel Islands, California, and as far east as Japanese waters[15]. Given the large distances travelled, and the different migratory habits of immature and adult seals[15,16], it is unlikely that parents and immature offspring would encounter one another while away from the breeding areas. When seals return they tend to frequent their natal sites[17], making it possible for individuals to meet again in future seasons. Females are sexually mature between 3 and 6 years of age, having their first potential offspring during year 4 after a 1-year delayed implantation and gestation. Male sexual maturation also occurs between 3 and 6 years, but males are unable to compete for females until year 10 (ref. 15).

I tested the effect of time on mother–offspring vocal recognition using playback experiments that spanned three periods: within season (3–4-week delay), between seasons (1-year delay) and between several seasons (4-year delay). I tested within season effects because it is the most critical period for recognition, and concurrently, when pups experience maximal growth. If growth has a detrimental effect on the acoustic cues used for recognition, I would expect to see a decreased response to 'old' calls (where there was a 3–4-week lag between recording and playback) as compared with 'recent' calls (those with a 2–3-day lag). Responses to both of these treatments were expected to be greater than to 'control' calls (calls of familiar non-mothers and non-offspring). I found that both mother and pup vocal responses to the three treatments differed significantly (repeated measures analysis of variance (ANOVA) of mother's responses: $F_{2,10} = 3.78$, $P < 0.05$; and pup's responses, $F_{2,14} = 13.43$, $P < 0.0001$). Whereas recent and old pup calls elicited more responses from mothers than control pup calls, responses to these two categories were not distinguishable from each other (paired *t*-tests: recent compared with control, $t_{10} = 2.97$, $P < 0.05$; old compared with control, $t_{10} = 2.96$, $P < 0.05$; recent compared with old, $t_{10} = 0.28$, $P > 0.05$). The same pattern was true for pup responses to their mother's calls (paired *t*-tests: recent compared with control, $t_{14} = 4.18$, $P < 0.001$; old compared with control, $t_{14} = 4.74$, $P < 0.001$; recent compared with old, $t_{14} = 1.83$, $P > 0.05$). This experiment shows that a short time lag of 3–4 weeks, double the maximum separation time naturally experienced during female foraging trips when lactating, does not affect vocal recognition.

To test whether recognition was maintained over consecutive seasons, I measured mother and pup vocal responses to playbacks of their offspring or mother's calls recorded the previous year. Test treatments were matched with year-old control calls. I found that both mothers and pups responded more to the year-old calls of their offspring or their mothers than to control calls (paired *t*-tests: mother responses, $t_5 = 2.7$, $P < 0.05$; pup responses, $t_5 = 6.71$, $P < 0.01$) showing that vocal recognition can be maintained for at least 1 year.

To test recognition after multiple seasons, I conducted playbacks to 4-year-old females during their first observed visits to the breeding area since they were neonates. I was able to measure the responses of four such females to playbacks of their mother's calls made when the subjects were pups. As before, test treatments were matched with similar aged control calls. None of the females had an offspring, appeared pregnant, or was seen to associate with an older female that could have been her mother. Each one remained on land for a maximum of 3 days and afterwards was not observed again. Each of the four females orientated to the test treatments and not to the control treatments (paired sign test: $P < 0.01$, $n = 8$; 2 playbacks to each of 4 subjects[18]). Two of the four females also responded vocally to the playbacks (insufficient for statistical comparisons). These two females called only to the test treatments and not once to the control treatments (the first female called during only one trial, and the second called during three trials). The specific vocal