swimming. Along with stimulation experiments showing short-latency spinal-oculomotor connections, these findings demonstrate that spinal neurons bypass the vestibular nucleus to make direct connections to the circuits driving eye movements (Figure 1B).

These experiments were conducted primarily in head-fixed preparations, leaving open the major question of how normal vestibular signals might combine with efference copy information to drive ocular reflexes. This question is at the heart of the puzzle of how the brain combines sensory signals about the *results* of self-motion with internally generated efference copy signals about *predicted* self-motion.

To address this issue, the authors performed a technically demanding set of experiments in the intact, immobilized tadpole. First they measured the oculomotor activity driven by sinusoidal rotation around a vertical axis (that is, as though the tadpole were on a turntable). The resulting vestibular signals indeed drive appropriate compensatory oculomotor activity. Next they checked that fictive swimming also drives oculomotor circuits, consistent with the other findings in this paper. Finally, they combined the two signals: sinusoidal rotation at one frequency simultaneous with fictive swimming at a higher frequency. The result? The oculomotor response is entirely driven by swimming efference copy, with no contribution from vestibular signals in the horizontal plane.

The fact that vestibular signals are dispensable for corrective eye movements during locomotion is surprising. What are the vestibular inputs doing? One potential answer provided by this work is that the vestibular signal cancellation appears to be selective for the horizontal plane. When the preparations were manipulated with a roll stimulus (one ear up and one ear down), vestibular signals were additive, albeit somewhat sublinearly, with efference copy signals. The implication is that vestibular inputs are unmasked when sensory feedback from movements does not match that predicted by a *task-specific* efference copy signal.

These findings share some similarities with an important series of experiments in monkeys by Cullen and Roy [4], who demonstrated that firing in the vestibular nuclei is tightly correlated with head velocity during passive, experimenter-driven head movements — but this activity is absent during active, animal-driven movements. Thus, it appears that in both systems the animals use an internally generated model of movement to suppress central vestibular signaling (Figure 1B).

A major open question going forward is the identity of this suppressive circuit. In fact, there are likely to be several such circuits. Studies in monkeys suggest that vestibular cancellation is selective for expected movement: suppression occurs only when 'proprioceptive' sensory input from neck muscles matches expected neck motion [5]. In contrast, the current study [2] shows that tadpoles cannot process even unexpected horizontal vestibular signals during swimming, suggesting a less selective circuit mechanism. Tadpoles and fishes lack trunk muscle spindles [6], leaving open the possibility that mammals evolved a more selective proprioception-based suppression circuit. The circuit basis of either a general or a selective suppressive mechanism will be important for understanding how the brain fuses self-generated and external information about movement.

What is the relevance of these findings in tadpole to mammalian oculomotor control circuits? If visual acuity relies progressively more on efference copy signals as locomotion speeds up, vestibular signaling could become less relevant at faster speeds. Indeed, humans with vestibular deficits are paradoxically more stable during running than during walking [7,8]. Thus, spinal circuits may influence not only local musculature, but the entire way we see the world.

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Department of Neurobiology, Northwestern University, Evanston, IL 60208, USA.
E-mail: david-mclean@northwestern.edu

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Evolution: Mitochondrial Burden on Male Health

In many animal species, males suffer more from age-related disease than females. Is there a common cause for this burden on male health? Recent work supports the theory that the female transmission of mitochondria disproportionately increases the mutation load in males.

Steven A. Frank

Mitochondria usually pass from mother to offspring, while males rarely transmit mitochondria. Selection is, therefore, blind to male-specific mitochondrial phenotypes. A mutation with a strongly deleterious effect in males but only a weak effect in females is nearly neutral, because only the female-specific consequences can be selected. This sex-biased 'selective sieve' inevitably causes deleterious mitochondrial mutational effects to accumulate more strongly in males than in females [1].

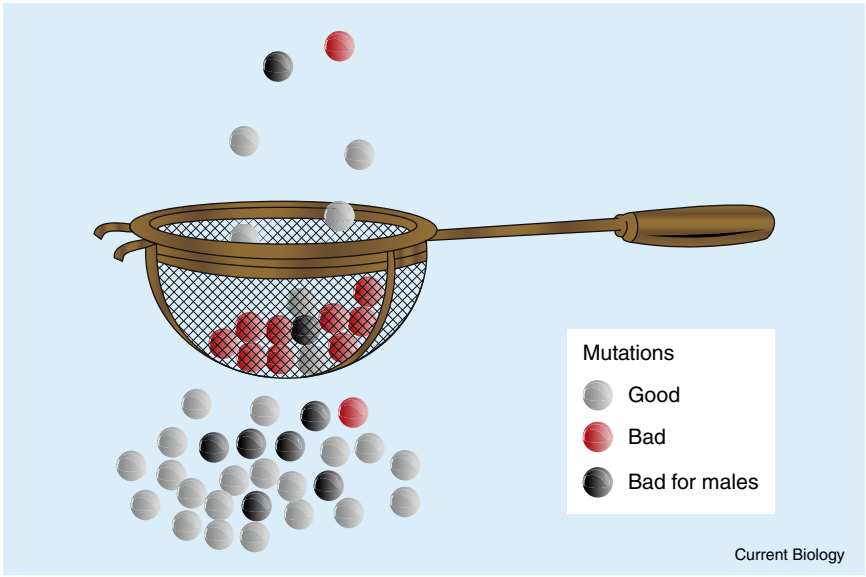

Figure 1. The sex-biased selective sieve.

Mitochondria are transmitted only by females in most animal species. Because males usually do not transmit mitochondria, a mitochondrial mutation that is deleterious in males and has little effect on females cannot be removed from the population by selection. In the figure, good mutations (white) pass through the selective sieve. Bad mutations (red) that reduce female fitness are usually removed by the selective sieve independently of whether those mutations also affect males. Bad male-specific mutations (black) usually pass through the sieve, because selection acts only on female-specific effects. Ultimately, male-specific deleterious mutations accumulate much faster than mutations that affect both sexes or affect only females.

But the actual force could in fact be weak and of little consequence. So, does this asymmetric selective sieve (Figure 1) truly impose a burden on male health? The answer is yes, according to a new study by Maria Camus, David Clancy and Damian Dowling [2] in this issue of *Current Biology*. They show that deleterious mitochondrial mutations accelerate male but not female aging in *Drosophila melanogaster*. The authors present these data as strong support for the sex-biased selective sieve theory. This conclusion arises from a particular chain of reasoning to relate the theory to specific predictions and from a particular experimental design to test those predictions. In theory, sexually dimorphic characters provide the most likely targets for the selective sieve [1,3,4]. It is relatively easy for a deleterious mutational effect in a male-specific character to be nearly neutral in females. For example, sperm swimming can be strongly affected by mitochondrial metabolic capacity [5]. Mutations that affect sperm may have little effect in females, because other tissues typically tolerate modest declines in metabolic capacity without noticeable degradation in performance [6]. A recent study by Damian Dowling and colleagues [4] suggested that in *Drosophila melanogaster* the mitochondrial selective sieve primarily influences male reproductive tissues. Genetic differences in mitochondria caused altered expression of nearly 10% of gene transcripts in males but had little consequence for females. The affected transcripts were mostly male-biased in expression and concentrated in the testes and accessory male reproductive glands.

In their new work, Camus *et al.* [2] wanted to go beyond the strongly dimorphic reproductive tissues. How are broad aspects of male health — in particular aging — influenced by the sex-biased sieve? Aging is perhaps the most widespread distinction between the sexes in overall vigor. In particular, mortality often rises more rapidly with age in males than in females [7]. How can one determine if the sex biased effects of mitochondrial mutations influence the sex differences in aging? Camus *et al.* [2] developed two predictions under the sex-biased sieve model. First, between different populations, males should express greater differences in mitochondrial effects on aging than females. Variation in female-specific effects between populations should be small, because selection efficiently purges deleterious effects in females. By contrast, significantly deleterious effects in males may be nearly neutral and fluctuate randomly, causing divergence between populations. Second, Camus *et al.* [2] predicted a positive association between mitochondrial nucleotide divergence and phenotypic divergence in male aging. As a population accumulates more mutations that are nearly neutral in females, it is likely to accumulate more deleterious phenotypic effects in males.

To test these two predictions, however, one cannot simply measure differences between populations. Suppose that the sex-biased sieve does accumulate male-specific deleterious mutations in mitochondria. Compensatory mutations in nuclear genes would be strongly favored to mask the deleterious mitochondrial effects in males [3]. Each population could have its own history of mitochondrial mutations with deleterious effects in males and compensatory changes in nuclear genes. Different populations might end up being similar phenotypically, but divergent with respect to their interactions between nuclear and mitochondrial genes. In consequence, one clearly needs to control the nuclear background. Through the miracle of widely available *Drosophila melanogaster* stock cultures, Camus *et al.* [2] obtained a reference nuclear background type, w^{1118}, and performed further sibling crosses to purify and maintain that nuclear background in the experiments. They also obtained 13 *D. melanogaster* lines from diverse locations around the world.

The experiments followed a mating regime to place the different mitochondria sampled from the 13 worldwide populations onto the standardized nuclear background. Male and female aging was measured by separating the sexes at birth, mating each sex to a standardized line of the opposite sex at day four, and then placing 30 mated individuals into each

vial, still separated by sex. Mortality was recorded during transfer to a fresh vial every second day. The experiment measured mortality for a total of 11,049 individuals. It turns out that male longevity was more variable than female longevity across the 13 mitochondrial lines. The reported statistical analyses compared the variability of males (and females) among populations against a null hypothesis of no variability. The male test was statistically significant while the female test was not. The authors also calculated the rate of senescence, which describes how fast the age-specific death rate increases with age. Again, the variability among male populations was significantly different from zero, whereas the variability among the female populations was not significantly different from zero.

Mitochondrial genotypic data supported the predicted positive association between genetic and phenotypic divergence. Camus *et al.* [2] analyzed each pairwise comparison among the 13 mitochondrial lines. They found a significant association between the number of amino acid changing nucleotide substitutions in the mitochondrial genomes of a pair and the phenotypic divergence in male longevity and rate of senescence. In this genetic test, one does not get a direct measure of the increase in senescence associated with deleterious mitochondrial mutations. Instead, each pairwise difference in the number of amino acid changes provides only a symmetric measure of divergence, because one does not have a way to determine which mitochondrial type has relatively more amino acid substitutions than the other. Nonetheless, the observed association does establish that genetic differences in mitochondria correlate with phenotypic differences in male aging.

Overall, the study by Camus *et al.* [2] shows the potentially powerful consequences of the sex-biased sieve acting on mitochondrial mutations (Figure 1). Many other aspects of genomic evolution and male disease may be influenced by this process. For example, Ruiz-Pesini *et al.* [8] analyzed mitochondrial genotypes associated with human male infertility caused by poor swimming of sperm and found a significant association between mitochondrial genotype and sperm swimming performance. Focusing on the common genotype in poor swimming sperm, Ruiz-Pesini *et al.* [8] evaluated the activity of three mitochondrial proteins in the electron transport chain. Complexes I and IV are partially encoded by mitochondrial DNA and had reduced activity. By contrast, complex II is entirely encoded by nuclear DNA and had normal activity. Thus, the sperm with relatively poor swimming ability were associated with a particular mitochondrial genotype and had reduced efficiency in mitochondrially encoded components of electron transport. In this case, the sex bias in mitochondrial fitness effects may arise because sperm swimming capacity is closely associated with metabolic efficiency [5], whereas small changes in metabolic efficiency seem to have limited phenotypic consequences in most other tissues [6]. Females, of course, lack sperm and so may be relatively insensitive to the consequences of the particular mitochondrial mutations that reduced sperm motility.

Another interesting consequence of the sex-biased sieve may arise from nuclear compensation. As deleterious male-specific effects in mitochondria accumulate, selection strongly favors nuclear variants that mask the effects of mitochondrial mutations [3]. Such compensation could lead to rapid divergence between populations in nuclear-mitochondrial interactions. If so, crosses between populations may lead to hybrid incompatibilities between nuclear and mitochondrial variants.

The study by Camus *et al.* [2] shows how very difficult it is to determine the importance of a particular evolutionary force in shaping complex phenotypes and complex genetic interactions within genomes. How could we, for example, determine the relative contribution of the sex-biased mitochondrial sieve to human male infertility and heart disease? How could we analyze any non-model species in which we lack the genetic tools to study mitochondrial effects against a standardized nuclear background? What is the way forward for this subject? At present, the best approach may lie in further studies on model organisms, such as *Drosophila*. Those studies could map out the scope and limitations of the sex-biased sieve's consequences. A mutational screen might provide an estimate for the fraction of mitochondrial mutations that are nearly neutral in females but deleterious in males [1]. One might also get a sense of the kinds of male traits affected by new mitochondrial mutations. It would, of course, be particularly valuable to know the specific mechanisms of gene action and phenotypic effects for mitochondrial mutations with sex-biased consequences. Once we have a clearer idea about what can happen in a few model species, we may be able to evaluate the prevalence of sex-biased effects for mitochondrial mutations in other animals. Male infertility is a particularly interesting phenotype, because of the clear potential for sex-biased effects, as illustrated by Ruiz-Pesini *et al.*'s [8] intriguing study of sperm defects. It might also be interesting to evaluate the sex-specific consequences of mitochondrial mutations with respect to diseases that are particularly prevalent in males relative to females. Heart disease comes to mind. Other male-biased diseases may also lead back to mitochondria.

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Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697, USA.
E-mail: safrank@uci.edu

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