# The odds of losing at genetic roulette

James F. Crow

**The number of harmful mutations that arise in each generation has been measured, and it is surprisingly high. This supports one theory of why evolution favours sexual reproduction, but the consequences for human health are unclear.**

The rate at which deleterious mutations occur in a genome is clearly a quantity of interest — not least when the genome is our own. It becomes particularly important if, as some have argued[1], the rate in some species is high, at several new mutations each generation. Yet the deleterious mutation rate has been notoriously difficult to measure, and no convincing estimates exist for any vertebrate. On page 344 of this issue[2], Eyre-Walker and Keightley give the first such estimates for ourselves, chimpanzees and gorillas.

Getting an estimate of the total mutation rate is relatively simple. Neutral mutations — those which neither enhance nor impair the organism carrying them — accumulate through the generations at a rate equal to the mutation rate[3]. The mutation rate can be determined by the rate of change of presumed neutral regions: areas of the genome, such as introns and pseudogenes, which are not translated into proteins. For mammals, these rates, extrapolated to the whole genome, lead to enormous numbers, on the order of 100 new mutations per individual[1]. Of course these can't all be deleterious, but no one knows what the proportion is. This proportion could be determined in principle by comparing the slower rate of evolutionary change of the genome as a whole with the faster rate expected under neutral assumptions; but this involves statistical uncertainties and extensive sequencing[4].

Eyre-Walker and Keightley[2] have made the analysis feasible by concentrating on protein-coding regions. They measured the amino-acid changes in 46 proteins in the human ancestral line after its divergence from the chimpanzee. Among 41,471 nucleotides, they found 143 nonsynonymous substitutions — mutations where swapping one DNA base for another changes an amino acid, and therefore the final protein made by that gene. If these had evolved at the neutral rate, 231 would be expected. The difference, 88 (38%), is an estimate of the number of deleterious mutations that have been eliminated by natural selection and have therefore made no contribution to contemporary populations.

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Figure 1 **Each member of each generation of humans probably has several harmful new mutations in their genome. It is likely that sexual reproduction is the cause of their elimination. Bdelloid rotifers (left), however, seem to have done without sex and genetic recombination for millions of years, and have been described by John Maynard Smith as an "evolutionary scandal".**

Translating these numbers into mutation rates gave a total rate of 4.2 mutations per person per generation, and a deleterious rate of 1.6. The rates for chimpanzees and gorillas were very similar, the deleterious rates being 1.7 and 1.2, respectively. The authors took 60,000 as the gene number and 25 years as the generation length. The number 1.6 is probably an underestimate, for various reasons. For instance, mutations outside the coding region are not counted and some of these regions — such as those controlling gene expression — are expected to be subject to natural selection. The gene number may also be an underestimate. If there have been mutations that increase fitness, they would also cause the number of deleterious mutations to be underestimated. A less conservative, and probably more realistic, estimate doubles the value, giving 3 new deleterious mutations per person per generation.

What's the significance? Every deleterious mutation must eventually be eliminated from the population by premature death or reduced relative reproductive success, a 'genetic death'[5]. That implies three genetic deaths per person! Why aren't we extinct? If harmful mutations were eliminated independently, as in an asexual species, it has been estimated that this would lower population fitness to a fraction $e^{-3}$, or 5%, of the mutation-free value[6], leading to the inevitable extinction of species with limited reproductive capacity. A way out is for mutations to be eliminated in bunches. This happens if selection operates such that individuals with the most mutations are preferentially eliminated, for example if harmful mutations interact. But such a process can only work in sexual species, where mutations are shuffled each generation by genetic recombination[1,7] (Fig. 1). The existence of a high deleterious mutation rate strengthens the argument that a major advantage of sex is that it is an efficient way to eliminate harmful mutations[1]. It also raises again the possibility of fitness decline or even extinction in rare species from too many harmful mutations[8].

Presumably, we humans have profited in the past by sexual reproduction's ability to reduce the effect of a high mutation rate on fitness. In the recent past the intensity of natural selection has been greatly reduced, especially where a high standard of living means that most infants reach reproductive age. From this it would seem that natural selec-

tion will weed out mutations more slowly than they accumulate. This effect may be accentuated by trends for males to start or continue reproducing later in life, because the sperm of older men contains more base-substitution mutations[8]. In a time of rapid environmental improvement, how this genetic decline will affect our health can only be guessed at.

Eyre-Walker and Keightley[2] noticed that the proportion of harmful mutations in the 46 genes in their study is greater in humans than in the equivalent genes of rodents. Their preferred explanation is that slightly deleterious mutations have become fixed in the population, by a process known as random genetic drift, during periods of human history when the breeding population size was low — especially during genetic 'bottlenecks'. This would increase whatever effect the accumulated mutations are having on current human welfare. Are some of our headaches, stomach upsets, weak eyesight and other ailments the result of mutation accumulation? Probably, but in our present state of knowledge, we can only speculate. □

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1. Kondrashov, A. S. *J. Theor. Biol.* **175,** 583–594 (1995).
2. Eyre-Walker, A. & Keightley, P. D. *Nature* **397,** 344–347 (1999).
3. Kimura, M. *The Neutral Theory of Molecular Evolution* (Cambridge Univ. Press, 1983).
4. Kondrashov, A. S. & Crow, J. F. *Hum. Mutat.* **2,** 229–234 (1993).
5. Muller, H. J. *Am. J. Hum. Genet.* **2,** 111–176 (1950).
6. Kimura, M. & Maruyama, T. *Genetics* **54,** 1337–1351 (1966).
7. Crow, J. F. *Proc. Natl Acad. Sci. USA* **94,** 8380–8386 (1997).
8. Lande, R. *Evolution* **48,** 1460–1469 (1994).

**Solid-state lasers**

# Lasing from a molecular sieve

**Stephen R. Forrest**

Lasers using organic dyes suspended in solution have been a fixture in optics labs for more than 30 years. They have high output powers and broad tunability over the entire visible spectrum, finding many applications, for instance in molecular spectroscopy. Another type of organic laser is now described by Vietze and co-workers in *Physical Review Letters*[1], one that has a remarkable property — the organic molecule is not suspended in solution, but rather is tucked away in the microscopic pores of a zeolite crystal. This 'microlaser' is one of a growing class of optically excited organic lasers that may eventually replace the messy and cumbersome liquid-dye laser, and indeed may find completely novel applications in optical sensing and communications, and in consumer devices such as printers and scanners.

Since the late 1960s, researchers have periodically attempted to make solid-state lasers based on organic dye compounds[2–4]. The reason is that, like solid-state lasers based on such inorganic semiconductors as gallium arsenide, organic diode lasers may give birth to a new generation of devices which have high power and, like their liquid dye cousins, can generate light across the visible spectral region.

In its simplest form, a laser is an optical resonator consisting of a gain medium placed in an optical cavity. The gain medium is a material such as an organic dye molecule that can, if sufficiently excited, amplify the intensity of a light beam passing through it; that is, a photon travelling through the excited medium stimulates the emission of additional photons which are 'in phase', or coherent. If the gain medium is placed between mirrors forming an optical cavity, a feedback path for the amplified optical beam is established, allowing a single photon to travel many times through the amplifying medium before leaving the cavity. These multiple round trips result in the build-up of a very high optical intensity characteristic of lasing. Early work largely involved placing pure organic crystals in a bulky external optical cavity[3]. These lasers had many of the disadvantages of cumbersome liquid dye lasers, and they tended to be short lived because the fragile organic molecules were exposed to the intense optical field in the cavity.

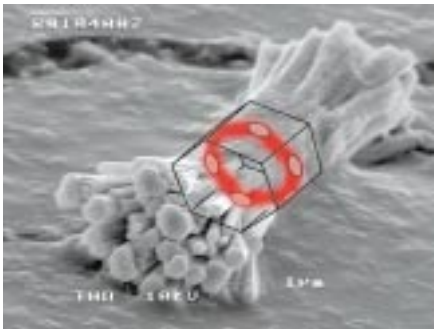

Figure 1 **Scanning electron micrograph of a microcrystal laser produced by Vietze *et al.*[1]. The hexagonal middle section forming the optical resonator, which provides feedback by total internal reflection (the so-called whispering gallery mode), is shown in outline.**

Very recently, advances in electrically-pumped organic light-emitting devices, which are used in bright, flexible, colour flat-panel displays, resulted in a renewal of interest in organic solid-state lasers (see ref. 5 for a review of light-emitting devices). The materials used in these thin-film devices luminesce efficiently when optically or electrically excited, have long operational lifetimes, and are reasonably good electrical conductors. Hence, the attraction of making simple, very small lasers using these materials. Demonstrations of lasing so far have been confined to films that are optically rather than electrically excited[6,7] (that is a second, intense laser source optically 'pumps' the thin film). Although this is an important step towards realizing an organic laser diode, the ultimate goal is electrical excitation, which would eliminate the large, external pump laser, producing molecular lasers that are tiny, but intense, sources of light.

The success of an organic laser diode will depend on reducing the electrical current needed to induce lasing — high currents can heat the molecular materials, degrade the contacts or otherwise damage the fragile thin films leading to an unacceptably short device lifetime. One way of reducing this lasing threshold is to shrink the optical cavity so that only a single optical 'mode', or wavelength, can be contained between the mirrors. These so-called microcavity lasers have taken many forms such as the 'organic vertical cavity surface emitting laser'(OVCSEL) demonstrated in our laboratory[8], ring lasers formed by dipping an optical fibre in an optically active polymer[9], microdisk lasers[10], and even lasers employing photonic crystals[11].

Vietze *et al.*[1] have taken a different approach. They show that individual dipolar dye molecules of 1-ethyl-4-[4-(*p*-dimethylaminophenyl)-1,3-butadienyl]-pyridinium Perchlorat (or Pyridine 2) can be loaded into the minute (0.7-nm-diameter) pores of the $AlPO_4$-5 molecular sieve during synthesis of the zeolite. Investigation of the pyroelectric properties of the composite revealed that the dye molecules are not only aligned within the cavities of the zeolite but, on average, are oriented with their electric dipole moments in parallel. This orientation results in strongly polarized fluorescent emission. The composite zeolite–dye bundles form tiny microcavities, which operate much like the ring lasers formed around optical fibres — the waist of the bundle forms a cylinder, 25 μm in circumference, around which the optical mode can circulate to achieve the desired resonator structure (Fig. 1). This circulating action is often referred to as a 'whispering gallery mode', reminiscent of the familiar effect experienced in domed buildings where sound waves emitted from one side of the dome are easily heard at the opposite wall due to multiple echoes off the curved interior. Vietze *et al.* present clear evidence for lasing in their unusual microcavities, which emit a single optical mode at a wavelength of 687 nm marked by a threshold in optical pump intensity.

It is not surprising that the excitation threshold of these microcavities is small — Vietze *et al.* report that a 12 nJ optical pump