

Sex frees viruses from genetic ratchet.

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EVOLUTION

ARNHEM, THE NETHERLANDS --It's probably the only question that the celebrated sexologists Masters and Johnson didn't ask: How did sex originate? Evolutionary biologists, however, have puzzled for much of this century over why so much of life has evolved the ability to shuffle genetic material between individuals--the essence of sexual reproduction. "It must confer some benefit," Lin Chao, an evolutionary biologist at the University of Maryland, College Park, said at a meeting of the European Society for Evolutionary Biology here in August. He then went on to report some of the first experimental evidence supporting one explanation, proposed 3 decades ago: that sex enables a population to free itself of harmful genetic mutations.

Chao gathered his evidence in one of the simplest of all sexual organisms, an RNA virus whose rapid mutations and short generation time put evolution on fast forward. "He's developed a clever experimental system to test a classic question in evolution," says Peg Riley, an evolutionary biologist at Yale University. "And he's got strong results" that support the hypothesis.

In the early 1960s, evolutionary theorist Hermann J. Muller argued that small, asexual populations would necessarily decline in fitness (or reproductive success) over time if their mutation rate was high, because they would accumulate harmful mutations. Muller proposed that this process would work like a ratchet, with each new mutation irreversibly eroding the population's fitness. Sex could provide an escape from the ratchet, he said, because recombination lets an organism reconstruct a mutation-free genome from two genomes that contain different mutations.

But devising a method to test the idea requires more than your garden-variety lab animal. Besides short generations and rapid mutations, the organism needs to be able to reproduce sexually as well as asexually. "You can't see the advantage of sex, unless you can withdraw that advantage," says Chao. Certain RNA viruses, he notes, fit the bill on all counts.

Chao chose to work with the ϕ 6 virus, which infects bacteria. The ϕ 6 genome is made up of three RNA segments, and virus "sex" consists simply of reshuffling these segments with those of another virus that has infected the same cell. Although segment swapping differs from the sexual reproduction technique of eukaryotes, it still produces a hybrid progeny and "so is another form of sex," Chao says.

But there was no joy of segmented sex for Chao's Phi 6 viruses. Instead, by some careful chaperoning, he forced them to reproduce asexually. He began by infecting a bacterial host with a single virus. As soon as this virus began to reproduce, he randomly selected just one of its progeny and used it to infect a new bacterial cell. The virus never had a chance to reshuffle its segments with those of another particle that had infected the same cell. "We pushed them through 40 of these bottlenecks," says Chao.

At this stage, Chao suspected that Muller's ratchet probably had a firm lock on the virus, impairing its reproductive fitness--a hunch he confirmed by placing one particle of the bottleneck virus and one of the original virus in fresh bacterial cultures for a day to see which reproduced more abundantly. In 20 such reproductive-competition bouts, the original strain of the virus always won. Next, Chao allowed different reproductively enfeebled viral populations to co-infect the same cells and reproduce sexually with each other. In about 30 generations, they had regained much of their reproductive fitness.

But was their renewed fitness actually due to sex, or simply the result of new mutations that made up for the deleterious ones? To answer this question, Chao staged a fresh series of experiments. In one, he crossed reproductively handicapped viruses with themselves to create a large population of "selfed" viruses. He then allowed the viruses to evolve freely over 30 generations. Because this population was not passing through bottlenecks, beneficial mutations would be likely to accumulate. But because the particles had nearly identical genomes, sex wouldn't offer any advantage.

The selfed virus increased its fitness by 21% compared to its original, reproductively deficient ancestor. "That increase was solely due to the virus's high mutation rate," says Chao. But when he added the benefits of sex by allowing the selfed virus to interbreed with other populations, the resulting population gained another 9% in fitness.

"We knew that the virus could recover its fitness from mutations alone," says Chao, "and people used to think that this effect would be so great, it would swamp out any advantage of sex." But that was not the case. "[The study] shows that sex is advantageous," he says. Riley adds that in Chao's experiment "sex does affect Muller's ratchet; it provides an escape"--which is just what most sex researchers have always said.

DIAGRAM: Even viruses do it. Viruses from two strains infecting the same cell can recombine whole chromosomes (right) or swap chromosome segments (left) in their offspring.

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## **Viruses scout evolution's path**

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ARNHEM, THE NETHERLANDS --Sex can lead to many things--even the merging of two seemingly incompatible evolutionary theories. So says Lin Chao of the University of Maryland, College Park, who realized that the fast-evolving viruses he uses to test theories about the evolution of sex (see previous story) could help settle another debate. At a meeting of the European Society for Evolutionary Biology here in August, Chao described how the viruses pointed to a possible resolution of a decades-old dispute about the trajectory of evolution.

R. A. Fisher of Cambridge University had argued in the 1930s that evolution is like a staircase, on which organisms evolve through a series of small genetic steps, each one leading to a higher level of fitness. They continue to climb the same staircase, refining existing adaptations, unless a dramatic shift in the environment forces them to begin scaling a different set of stairs. In contrast, Sewall Wright, working at about the same time at the University of Chicago, imagined that genetic changes, as well as environmental ones, could derail the evolutionary process. He pictured evolution as taking place on a landscape of numerous peaks and valleys. In his eyes, harmful mutations can displace an organism from a peak into a valley. In overcoming such mutations, organisms may begin climbing a new peak, setting them on a different evolutionary course.

Chao's virus cultures suggested that both metaphors may be valid. He and his graduate student Christina Burch had originally set out to test Fisher's model of adaptive evolution, which holds that large mutations that dramatically increase fitness are likely to be rare because such mutations tend to have large, deleterious side effects. "Fisher's model is such a pretty idea," says Chao, "because it makes a very strong, straightforward prediction." Yet despite its elegance, Chao notes, "good data to support it don't exist."

Chao and Burch thought they might find supportive data by experimenting with RNA viruses because of their breakneck evolution. They multiply 100-fold every hour or so and pick up many mutations along the way. To see if viral evolution matches Fisher's

model, the researchers studied a population whose members had all suffered from a deleterious mutation, which cut the number of progeny they produced. "We wanted to see how--either through large or small steps--it would regain its fitness via natural selection," explains Chao.

The researchers used populations of the severely mutated virus ranging in size from 10 to 10,000 particles. Each population was allowed to grow freely on a bacterial host. At the end of each day, Chao and Burch staged experiments comparing the test viruses with the original, unmutated strain to see how quickly the different populations were regaining their fitness.

In populations below 1000 particles, "fitness increased in multiple steps," Chao says, "which surprised and delighted us." In populations of more than 1000 particles, the virus came roaring back in one large step, presumably because large compensatory mutations were more common in the larger populations. But Chao argues that the combined results support Fisher, "because his model predicted that compensatory mutations of large effect would be rare, and that's exactly what we found. They don't occur except in very large populations."

Burch and Chao's experiment is "the first really serious empirical test of Fisher's model," says Bruce Levin, a population geneticist at Emory University in Atlanta. He adds that it shows "the power of using microbial systems to test general evolutionary hypotheses." But even if Fisher was right about the pace of evolutionary change, Chao adds, the results also support Wright's view that evolutionary shifts can occur without major environmental change.

The populations regaining their fitness via small compensatory mutations necessarily ended up at new adaptive peaks, says Chao, which represent different ways of attaining the same fitness. "The only way to go back to the same peak you started on" is via a "back mutation" that reinstates the gene in its original form--which should occur only in a single, big step, he explains. In contrast, "a compensatory mutation implies that you're headed toward a new peak." He adds, "At least in this one case, it seems that Fisher's model fits with Wright's view of an evolutionary landscape."

"It's absolutely intriguing," says Hope Hollocher, an evolutionary biologist at Princeton University. "Chao has opened the door toward merging these two viewpoints." She notes, however, that his experiments need some fine-tuning before biologists will be convinced that Fisher and Wright aren't always at odds.

PHOTO (COLOR): Pathfinders. Christina Burch and Lin Chao traced the course of evolution in viruses that infect these bacterial cultures.

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