No winners?

Investigators are pursuing a host of other lithographic schemes that create circuit patterns with everything from beams of ions and neutral atoms to arrays of miniature electron guns and atomic imaging probes (*Science*, 1 November, p. 723). Research also is under way on embossing resist layers on silicon wafers with miniaturized polymer stamps (*Science*, 5 April, p. 85). Still, some industry experts aren't optimistic about any of the technologies' market prospects.

The fundamental obstacles are not only technological but economic, says Abbas Ourmazd, a physicist and lithography expert at the Institute for Semiconductor Physics in Frankfurt, Germany. Silicon technology is driven by cost reduction, and soon, economic incentives for packing more transistors on chips may evaporate, contends Ourmazd. As the number of devices integrated on a chip increases, each additional device represents a smaller fraction of the total, thus providing a smaller economic benefit, he says. At the same time, as the number of devices per chip goes up, so does the chance that a chip will contain enough defective transistors that it has to be discarded. These economic realities aren't new. In fact, researchers have long sought to counter the creeping increase in the discard rate by making lithographic systems ever more reliable. But achieving the added reliability is becoming increasingly costly, says Ourmazd, which is why he thinks the big shrink may exhaust itself by about 2010.

He's in the minority, though. According to Bijan Divari, a silicon integration expert at the IBM Semiconductor Research and Development Center in East Fishkill, New York, smaller has meant better for over 30 years, and that probably won't change for a while. With just the feature-size reductions promised by the optical systems under development, chip designers will, for the first time, be able to fully integrate the two principal types of device functions—logic and memory—into a single chip. Says Divari, "That [alone] could have a tremendous [economic] impact. The economics of integration ... warrants the pain we have to go through to come up with new lithographic techniques." As long as these economic incentives don't disappear, chipmakers may have a shot at extending the life of Moore's Law.

–Robert F. Service

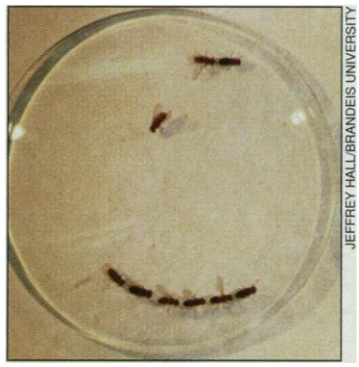
In an upcoming issue, Science *will explore the new types of devices made possible by these technologies.*

GENETICS

Fly Sex Drive Traced to *fru* Gene

Humans are far from being the only animals with complicated sex lives. Take the fruit fly *Drosophila melanogaster*, in which males stalk the females and woo them with song before mating with them. Yet in the fly, at least, most of this complex repertory turns out to be controlled by a single gene.

Geneticist Jeff Hall of Brandeis University first showed in the 1970s that the gene, called *fruitless* (*fru*), influences sexual preference; males with a mutation in the gene court both males and females. But in the new study, which appears in today's issue of *Cell*, a multiuniversity team of researchers, including Hall, reports that males with more severe mutations aren't just indiscriminate, but sexless. That finding, along with evidence that the protein encoded by *fru* can turn other genes on and off and is present in only a handful of nerve cells, suggests that *fru* is a high-level regulatory gene that somehow equips specific centers in the brain to coordinate male courtship behavior, the scientists say.



JEFFREY HALL/BRANDEIS UNIVERSITY

Chain gang. Males with a mutant *fru* gene court each other, sometimes forming chains.

"It's a real breakthrough," says Dean Hamer, a researcher at the National Institutes of Health who studies whether sexual orientation in humans has a hereditary component. "It confirms what everyone suspected but no one had really proven—that sexual behavior can indeed be genetically programmed in an animal." But Hamer and other researchers caution that the study sheds little direct light on sexuality in *Homo sapiens*, because the genes influencing sexual differentiation in flies and mammals are unrelated.

Researchers have known for several years that four genes called *sex-lethal* (*sxl*), *transformer* (*tra*), *transformer-2* (*tra-2*), and *doublesex* (*dsx*) largely determine a fruit fly's sex. In females, *sxl* activates *tra* and *tra-2*, and the Tra and Tra-2 proteins splice *dsx* messenger RNA into a female-specific form. The Dsx protein made from this RNA then activates various genes lower on the genetic ladder that build female body parts. In males, *sxl*, *tra*, and *tra-2* are inactive, so default machinery splices Dsx RNA into a form encoding a male-specific protein.

In 1992, however, Oregon State University geneticist Barbara Taylor found that the growth of a specific muscle found only in male flies, the Muscle of Lawrence (MOL), is controlled by Tra and Tra-2, but not by Dsx. "That said there had to be a separate branch in the sex-differentiation gene hierarchy, analogous to the *dsx* branch" but regulating MOL development, Taylor explains.

Reasoning that the Tra proteins work the same way for the MOL-controlling gene as for *dsx*, Lisa Ryner, who works with Stanford University geneticist Bruce Baker, looked for other genetic sequences containing the target site used by Tra and Tra-2 to regulate *dsx* splicing. And she found a big one: a gene fragment that mapped to the same spot in the fly's chromosomes where Hall and postdoc Don Gailey had roughly located *fru* in genetic studies several years earlier. At the same time, Taylor found that females exposed to male Dsx acquire male anatomy but don't display courtship behavior, an indication that the MOL-controlling gene branch also influences behavior.

Using Ryner's gene fragment and other pieces of *fru* identified by developmental geneticist Steve Wasserman and graduate student Diego Castrillon at the University of Texas Southwestern Medical Center in Dallas, the Baker, Hall, Taylor, and Wasserman labs eventually cloned the entire *fru* gene, finding that the protein it encodes is likely a transcription factor, a protein that turns other genes on or off. An independent group led by geneticist Daisuke Yamamoto of the Mitsubishi Kasei Institute of Life Sciences in Tokyo also cloned part of the gene.

Consistent with *fru*'s proposed role in regulating male sexual behavior, the U.S. group now reports that the RNA making its protein product is spliced together in distinctive male and female forms by Tra and Tra-2, just as Dsx RNA is. And males with severe mutations in *fru* lose the will to follow other flies, play courtship songs on their wings, or attempt copulation, indicating that the gene somehow orchestrates these behaviors. Further supporting that idea, Taylor showed that *fru* is expressed primarily in nine small clusters of nerve cells, including several previously mapped by Hall as "courtship centers."

And that means researchers are "starting to get a handle on how the neural circuits that generate complex behaviors are put together," says Michael McKeown, a developmental geneticist at the Salk Institute in La Jolla, California. These circuits are bound to be even more complex in humans, McKeown says, but the latest insight into fruit fly sex is "a major step"—or maybe six—toward understanding them.

–Wade Roush