the accumulated variation could be unleashed, giving rise to dramatic differences in a population over a short period of time and perhaps even creating changes that could lead to new species.

Experiments in other labs on house flies and plants may have given this theory some backing, McDonald says. In those tests, inbreeding prompts widespread genetic variation, which may be an outcome of losing the suppression effect. McDonald's next step will be to determine how prevalent this kind of suppression is in natural animal populations.

Explaining the evolution of new species is a big problem in evolutionary theory, but at least speciation is something that has been documented. The third line of thought—and the biggest wild card in the speculation about the evolutionary ramifications of transposable elements—concerns the possibility that transposable elements might "jump," not just within one organism's genome, but from one species to another. Researchers haven't directly demonstrated this type of horizontal transfer of genetic material. But last September, Marilyn Houck of Texas Tech University, Lubbock, working with Jonathan Clark and Kenneth Peterson, who were then postdocs in Margaret Kidwell's lab at the University of Arizona, Tucson, presented a strong circumstantial case that a parasitic mite had carried transposable elements called P elements from one fruit fly species to another within the past century (*Science*, 6 September 1991, p. 1125).

This mite-borne method of horizontal transfer amazed researchers and led them to wonder whether such transfers could have had a significant influence on the evolution of higher organisms. But, as Kidwell reiterated at the meeting, the key question of how frequently this genetic sharing happens in nature is a long way from being answered. Until it is, she says, the evolutionary significance of genetic transfers between species will be a mystery.

So, while questions about transposable elements dramatically outnumber experiments—let alone answers—the cadre of scientists convinced that they are an important part of the genome continues to grow. It may have taken decades to recognize the importance of McClintock's work, but few today would dare to laugh at her jumping genes.

–John Travis

Additional Readings

B. McClintock, "Chromosome Arrangement and Genic Expression," *Cold Spring Harbor Symp. Quant. Biol.* **16,** 13 (1951).

J. McDonald,"Macroevolution and Retroviral Elements," *BioScience* **40**, 183 (1990).

D. Berg and M. Howe, Eds., *Mobile DNA* (American Society for Microbiology Publications, Washington, D.C., 1989).

The symposium papers will be published in the fall issue of the journal *Genetica*.

MEETING BRIEFS

Science Innovation '92: The San Francisco Sequel

Several weeks ago, *Science* and AAAS hosted an entirely new meeting in San Francisco: Science Innovation '92, designed to showcase the latest and hottest advances in technique, particularly in the field of biomedicine. In last week's issue, staff writer John Travis profiled a couple of the intriguing developments from the meeting. Now free-lancer Paul Selvin offers another pair–both having to do with the manipulation of DNA.

The Big Speedup

The disputes that the Human Genome Project engendered when it was conceived are largely gone. Few biologists today spend much time or energy asking whether the project is worthwhile. Instead, they wonder how to get the job done. And in that arena, the technical questions are just as daunting as the philosophical debates raised when the project began. "Procedures that are 10 to 1000 times more effective will need to be implemented if the human genome is to be successfully deciphered," says Leroy Hood of Caltech, one of the genome project's leaders.

But at the Science Innovation meeting, held in San Francisco from 21 to 25 July, two groups working independently announced they've made a dent in at least one part of the sequencing problem. A group led by Rich Mathies at the University of California, Berkeley, and one led by Lloyd Smith at the University of Wisconsin announced prototype machines that can sequence DNA five to 25 times faster than current, commercially available machines. That could be a significant gain, says Tony Carrano, director of the human genome center at the Department of Energy's Lawrence Livermore Laboratory, who hasn't yet had a chance to evaluate the new machines. "A factor of 10 [in speed] is very important." What's more, these new machines may be able to use significantly smaller amounts of DNA, which could help in automating, and speeding up, other parts of the sequencing process.

The key to both methods is a combination of advances in gel electrophoresis and in fluorescence detection of DNA. Gel electrophoresis is an essential step in sequencing DNA. In that method, fragments of DNA are put onto a gel; an electric field is applied to the gel, separating the fragments according to size. Ordinarily, the gels are relatively large (about the size of this page) and separation takes about 10 hours. Yet trying to make the DNA run faster by cranking up the electric field only results in overheating.

Three years ago, however, Smith found that he could run the DNA up to 26 times faster without heating problems if he packed the gel in thin capillary tubes. More recently he's found similar results using thin (25 to 100 microns thick) gel slabs, on which he can run 18 samples at once (soon to be 50). Mathies, along with postdocs Xiaohua Huang and Mark Quesada took the idea a step further, packing 25 capillaries side by side, with immediate plans to go to 100 or 150 capillaries.Both groups use techniques for detecting the DNA bands that are based on the most sensitive method, fluorescence, and therefore they can detect quite small samples of nucleic acids. In addition, both are working to develop means for automating the loading of DNA onto the gels in their procedures.

But even before these processes reach full automation, they've yielded some notable advances over the standard commercial methods. The Applied Biosystems Model 373, a widely available DNA sequencing machine, can handle about 1350 bases per hour. By comparison, Mathies' system can sequence 5300 bases per hour, and he argues that it could readily be speeded up to 35,000 bases per hour. Smith's speedster is now up to 9300 bases per hour, with a 26,000 bases per hour machine in the works. Both groups emphasize that the increase in speed comes without a loss in accuracy.

Aside from their raw speed, these contraptions could have an important secondary benefit for the big-time sequencers. If the loading problems can be solved, the machines' ability to make do with smaller amounts of DNA could help to accelerate the sample-preparation process. And in many cases that is now the limiting step. "Of the thousands of sequencing projects in the world, it's fair to say that the number of projects in which the machine is limiting could be as few as three," says a knowledgeable source who demanded anonymity to avoid offending colleagues. He adds that "most people don't realize [that sample preparation is often the problem], and the new machines may help publicize this fact and so spur people into developing faster ways of preparing the DNA."

But in order for these benefits to be reaped in practice, these new devices will have to make it into the commercial arena. And whether these machines can be commercialized remains, for now, an open question. Early

on, Applied Biosystems turned down both groups, although Mathies says he is now in negotiations with a biotech company aimed at licensing his technology. So for the moment, the intrepid adventurers of the human genome will have to keep waiting for the tools that will make their dream a practical possibility.

The Dyer's Hand

Although a child may love his yo-yo, and the Wizard of Oz's Dorothy surely loved Toto, you wouldn't think those affections would have any particular relevance to molecular biology. But molecular biologists are sure to love a new pair of creatures with the whimsical names of YOYO and TOTO. At the Science Innovation conference, researchers reported development of these two new DNA dyes, which, cute names aside, have achieved an important technical milestone: They can detect minute amounts of double-stranded DNA—as small, in fact, as radioactive probes—but without the danger or mess inherent in radioactivity. As a result, they have the potential to make significant contributions to genome mapping and DNA fingerprinting, among other applications.

YOYO and TOTO have "the charm of simplicity," says Alex Glazer, who along with graduate student Hays Rye and others developed these dyes at the University of California, Berkeley, in collaboration with Stephen Yue and Richard Haugland at Molecular Probes Inc.

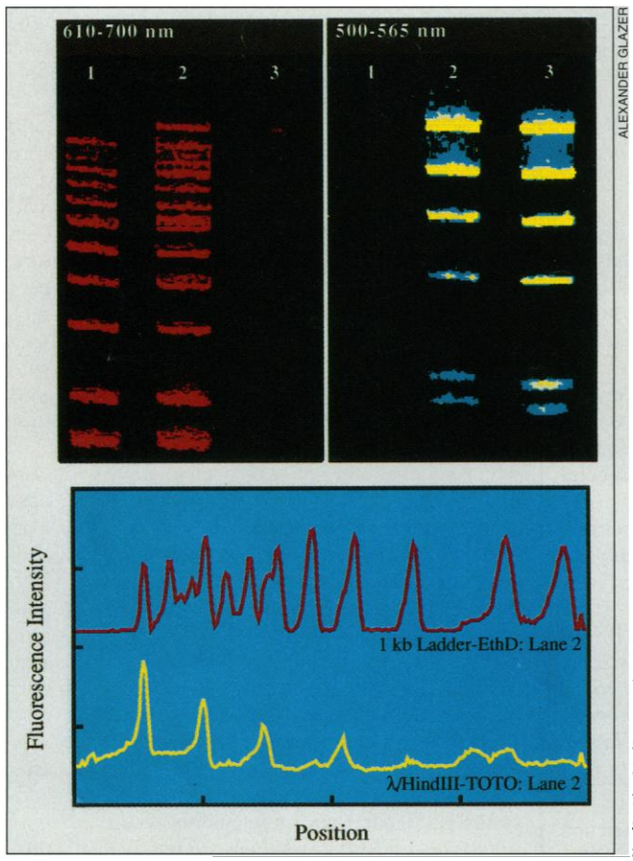
And the inventors aren't the only ones touting the dyes. "I really see the future as being very bright for these molecules," says Jasper Rine, head of the Department of Energy's Human Genome Project at the Lawrence Berkeley Laboratory. "As a replacement for radioactive detection of small quantities of DNA, they have the capacity to make major improvements in genome research," he says.

The reason for the enthusiasm is that for years researchers have been looking for alternatives to radioactive probes for detecting DNA. Although radioactivity is currently an indispensable tool because of its unsurpassed ability to label and detect small amounts of material, it's a four-letter word to biotech entrepreneurs and managers of big efforts such as the Human Genome Project. Radioactive methods are dangerous in the hands of semiskilled workers, and they are hard to automate; they're expensive, awkward, and time-consuming; finally, radioactivity is highly non-politically correct, environmentally speaking. In search of replacements, scientists have used everything from fluorescent dyes to chemical reactions that give off light to the firefly's light-emitting molecules. Yet these alternatives either lack sensitivity or are cumbersome. "I've been attending nonisotopic meetings for a dozen years," says Irena Bronstein of Tropix Inc., who organized a session on alternatives to radioactivity at the innovation conference, "but radioactivity is still around."

Now come Glazer's dyes, which have the double charm of being easy to use and about 500 times more sensitive than often-used dyes like ethidium bromide. There is a catch, however: Using a simple light-box to excite the dyes yields only a 25-fold improvement over regular dyes, Glazer says. To get the full 500-fold improvement requires some moderately fancy equipment, including a laser and sensitive detectors. For that, Glazer turned to Rich Mathies, a spectroscopist in Berkeley's chemistry department. The result? The ability to detect a mere 4 picograms of DNA in a single gel band "as good or better than [using] radioactivity," says Mathies.

Behind that achievement lies a simple conceptual strategy: If a single DNA dye is good, a dimer of that dye should be better. In the 1970s Jean-Bernard Le Pecque and his colleagues took two ethidium bromide molecules, stuck them together with a short linker, and made "ethidium homodimer." The result was a vast improvement over conventional dyes. In the new round of work, Glazer and co-workers adopted the same strategy but started with even better dyes, oxazole orange (YO) and thiazole orange (TO), to make the dimers YOYO and TOTO. The results are dyes that absorb light unusually well, stick to DNA like glue, and fluoresce when bound to DNA but have virtually no fluorescence when not bound to DNA. All of which means plenty of signal and little background.

That's good news for biologists who work with small amounts of DNA. At LBL's genome center, staff scientist Alla Lishanskaya is already using the dyes in a new procedure to test for carriers of genetic diseases. She compares a patient's DNA with a complementary DNA strand of normal sequence by hybridizing them and looking for mismatches, which would indicate a mutation. But she has to work with small amounts of a patient's DNA—because amplifying the DNA by using many cycles of the polymerase chain reaction would introduce sequence errors in the DNA. Glazer's dyes let her use less DNA, and the result is fewer false positives.



ALEXANDER GLAZER

Living color. Having two ultrasensitive fluorescence dyes makes it possible to measure the length of DNA fragments with considerable consistency. The upper panels show two fluorescent images of a single gel, seen through two different colored filters. The images show that two samples labeled with different dyes (lanes 1 and 3) can be mixed together (lane 2) yet detected separately, improving the accuracy of length comparisons. The lower panel shows the peaks of fluorescence intensity.

And that's not all. Glazer points out that the new dyes could have important benefits for DNA forensics and genome mapping. In both fields it's important to measure the length of a specific DNA fragment by running it through a gel, which is often not easy to do accurately. Indeed, variations from gel to gel and from lab to lab in determining DNA fragment lengths have been one source of the controversy over DNA fingerprinting. Now, by using two of Glazer's dyes simultaneously, labs may be able to achieve greater accuracy than with current techniques—though Glazer concedes he's just started to examine the issue in depth. Having two supersensitive dyes makes it possible to run both a "control" DNA fragment of known length acting as a yardstick, labeled with one dye, and an unknown sample, labeled with the second dye. Such a procedure, not feasible with radioactivity, greatly improves precision and reproducibility. And that, along with the other potential uses for these new dyes, is enough to make many people involved in DNA detection light up.

–Paul Selvin

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