or can be coaxed into a vapor with bursts of energy from a laser or ion beam. But vaporizing large biomolecules while keeping them intact once seemed impossible. A decade ago, however, Franz Hillenkamp and colleagues at Westfälische Wilhelms University in Münster, Germany, found a way to do so with proteins: Cocrystallize them with certain small molecules, collectively called matrices. When a nanosecond laser pulse vaporizes the matrix, the resulting puff of material gently lifts the ionized biomolecule as well.

DNA was a tougher problem. But in 1993, Christopher Becker, then at SRI International in Palo Alto, California, and now at GeneTrace Systems in Menlo Park, California, found a simple matrix compound, 3-hydroxypicolinic acid, that worked with DNA sequences 20 to 25 bases long. By trial and error, MALDI practitioners have come up with several new matrices that work with DNA fragments as long as 100 bases.

The latest MALDI-TOF machines allow the cloud of matrix molecules to dissipate before applying an electric field. The field accelerates the charged DNA fragments toward a detector, and the differences in time of flight can reveal mass differences as small as 0.03%. If the DNA sequences from a gene have the same length—as they do if they have been produced by the polymerase chain reaction—any departure from the mass of the normal sequence reflects a mutation that has deleted or added bases or substituted others that have a different mass. "The results are an absolute indicator of the presence or absence of specific DNA sequences," says Sequenom's Little. MALDI-TOF can distinguish gene variants that differ by as little as a single base pair, and it can also analyze microsatellites—stretches of two-, three-, or four-nucleotide repeats often used as markers for locating disease-causing genes.

Besides offering unmatched precision, MALDI-TOF is inherently fast. The DNA forms a vapor and flies to the detector in fractions of a second; even repeating the process several times with the same sample to boost the sensitivity takes as little as 2 seconds. By preparing the samples in a grid and having the laser scan each spot in turn, a MALDI-TOF instrument can analyze 100 samples or more in a matter of minutes.

The combination of speed and accuracy could give the technique a role in genome sequencing as well as diagnosis. Standard, Sanger-type DNA sequencing generates many partial copies of a DNA sequence, each one starting at one end of the sequence and ending with a different one of the constituent bases. To determine the original sequence, biologists need to know the final base on each partial copy, together with the copy's length. Doing so now requires reading hundreds of bands on gels. But by sending the mixture through a mass spectrometer, biologists could quickly read off the fragments' lengths and—from the mass differences between successive fragments—the final base on each one. Investigators at both GeneTrace and Sequenom have published sequences determined with MALDI-TOF, the latest one, from Sequenom, appearing in the April *Nature Biotechnology*.

For practical gene sequencing, however, MALDI-TOF would have to work with DNA fragments much longer than the current 100-base capacity. Becker reportedly has discovered a new proprietary matrix that he expects will extend MALDI-TOF's reach to 1000-base sequences. "If you can really do upward of 1000 bases using this technique, and if it is indeed faster and cheaper, then this would be a big breakthrough for high-throughput sequencing," says Jeffrey Polish, who works in Mark Johnston's sequencing laboratory at Washington University in St. Louis.

In the meantime, the technology has no shortage of applications. Sequenom has shown, for example, that it can discriminate among 30 of the mutations that cause cystic fibrosis and pick up polymorphisms in the apolipoprotein E gene, which have been linked to familial hyperlipidemias, heart disease, and Alzheimer's disease. GeneTrace has developed a mass spectrometry–based system that can analyze which genes are being expressed in cells by identifying expressed sequence tags, short stretches of DNA copied from the messenger RNA made by active genes. Knowing which genes are active in a tissue can help pharmaceutical companies determine which ones are good drug targets.

With MALDI-TOF instruments running about $125,000 each—less than a standard clinical chemistry analyzer—these systems may also end up in large diagnostic labs. "Diagnostics at the level of the gene is something that we know is valuable, but is difficult, slow, and expensive today," says David Cooper, chief scientific officer at Nichols Institute Reference Laboratories, a division of Quest Diagnostics, one of the big 3 national reference laboratories. MALDI-TOF, he says, could be just the right medicine.

–Joseph Alper

Joseph Alper is a free-lance writer in Boulder, Colorado.

MATERIALS SCIENCE

Making a Bigger Chill With Magnets

LOS ANGELES—Refrigerator magnets are best known for holding shopping lists and old postcards onto refrigerator doors. But in a few years, much more powerful magnets could be the key to keeping food cold in so-called magnetocaloric refrigerators, which would be more energy efficient and less polluting than standard models. Now a new class of magnetocaloric materials, announced here last week at a meeting of the American Physical Society, could make these magnetic refrigerators more practical and versatile.

The magnetocaloric effect works when strong magnetic fields align quantum-mechanical "spins" of electrons within atoms. This transition reduces one aspect of the randomness, or entropy, of the atoms. But according to laws of thermodynamics, some other aspect of randomness has to increase in compensation, so the atoms increase the randomness of their velocities—vibrating and heating up. Once this heat is carried away by a coolant such as water, the field is removed and the effect works in reverse, chilling the material and cooling a refrigerator. To date, the peak performance has been with the element gadolinium.

By adding various amounts of silicon and germanium to gadolinium's crystal lattice, Vitalij Pecharsky and Karl Gschneidner of the Ames Laboratory at Iowa State University discovered a new class of materials that can chill two to six times further in a single magnetic cycle, meaning that the refrigerators could operate with weaker magnetic fields or less material. Depending on the germanium-to-silicon ratio, the new materials also operate from about room temperature all the way down to –253 degrees Celsius. The cold end of the range would allow magnetocaloric freezers to liquefy hydrogen or natural gas for use in clean-burning power plants or future automobiles.

To come up with the new compounds, the team followed up on hints that magnetocaloric materials containing gadolinium and either silicon or germanium—but not both—prefer a different range of temperatures than gadolinium alone. "We're not trying to come up with exotic new compounds out of the pure blue sky," says Gschneidner. The surprise, he says, was that the magnetocaloric effect turned out to be far larger when both germanium and silicon were added to the material.

"These new materials give you a lot more flexibility in designing magnetocaloric [refrigerators]," says Carl Zimm, a senior scientist in magnetic refrigeration at Astronautics Corporation of America in Madison, Wisconsin. The team is still working on making enough of the material to try it out in Zimm's prototype gadolinium-based refrigerator, which has been running for about a year. The test should take place "within a couple of months," says Gschneidner.

–James Glanz