High-Speed Materials Design

Materials scientists are applying techniques pioneered by drug designers to blend elements in thousands of different combinations and screen the resulting compounds for specific properties

Xin Di Wu was riding the kind of scientific wave most researchers only dream about. In 1995, as part of a team at Los Alamos National Laboratory in New Mexico, Wu helped discover a way to make one of the most promising high-temperature superconductors—normally a brittle ceramic—into a flexible wire. That development could pave the way for winding the material into coils for superconducting high-field magnets in everything from medical imaging machines to electric motors. But rather than ride that wave, last year Wu backed off and caught another rising swell that he thinks has the potential to grow even larger. "I wasn't looking for a job," says Wu. "But the opportunity to do something unique got me very excited."

Wu landed at a small Silicon Valley start-up called Symyx Technologies, a company that bills itself as the wave of the future for discovering everything from new catalysts to superconductors. The new approach to chemical discovery that Symyx hopes to exploit uses banks of robots and computers to systematically react chemical ingredients in thousands of different combinations at once, then test the products in hopes of finding blockbuster new compounds. It's a vision that has already transformed the way new drugs are discovered, turning the discovery process from a painstaking, one-molecule-at-a-time business to an industry where thousands of new compounds can be created and screened in just days. In less than a decade, this transformation has spawned a host of new drug-discovery companies and attracted hundreds of millions of dollars in investments.

Now Wu and others are betting that the same high-speed chemistry technique—known as combinatorial chemistry—will pay off in other research-intensive businesses, such as the chemical and electronics industries, that are constantly searching for new compounds that can improve existing products or lead to entirely new applications. Already, there are hints that Wu and his colleagues may have made a smart bet. Last month, the German chemical giant Hoechst AG announced an agreement to pay Symyx $10 million over 2 years, with the possibility of far more to come, for first rights to new catalysts being developed at the company. Large chemical and electronics firms such as DuPont, Kodak, and Lucent Technologies' Bell Labs have started their own exploratory efforts in the field. Others such as Dow Chemical and Engelhard, which produces catalysts, are watching to see whether they should jump in.

Industry insiders point out, however, that combinatorial chemistry's success in the new arena is no sure bet. Among the many problems: screening arrays of hundreds or thousands of newly created compounds to identify a few potentially useful ones. Perhaps even more worrisome is that new materials rarely command the same high prices as blockbuster drugs, all of which makes research planners cautious. "It's a potentially very useful technique," says Lawrence Dubois, director of the Defense Sciences Office at the Defense Advanced Research Projects Agency (DARPA) in Arlington, Virginia. "But a number of people [in industry] are waiting for the first breakthrough before jumping in."

X.-D. XIANG/LBNL

Glowing prospects. An array of different combinations of phosphors being screened for brightness in ultraviolet light.

Promises, promises

Similar cautions greeted the advent of combinatorial chemistry in the late 1980s. The technique made its industrial debut when entrepreneur Alejandro Zaffaroni set up a small company called Affymax in 1988 to turn out enormous collections of small, proteinlike molecules called peptides, which could then be tested for possible use as drugs. Because enzymes in the stomach readily break down peptides, many doubted that the strategy would be useful for making drugs. But when researchers at the University of California, Berkeley, and elsewhere began showing that the same techniques could be used to turn out libraries of more stable small organic molecules, similar to those that make up most therapeutic drugs, the industry embraced combinatorial chemistry. Just 7 years after its founding, Affymax was bought by the British pharmaceutical giant Glaxo Wellcome for $533 million.

Now Zaffaroni and Berkeley chemist Peter Schultz—co-founders of Symyx—see that history repeating itself. "We're back to 1988 to '89 in combinatorial chemistry in the pharmaceutical industry," with small start-ups jumping in with both feet and industrial giants wading in gingerly, says Schultz. "If combinatorial chemistry works so well with the few elements used in drugs, [such as oxygen, carbon, and hydrogen], why not apply it to the rest of the periodic table?" says Schultz, who also has a joint appointment at the Lawrence Berkeley National Laboratory (LBNL) in California.

Why not indeed. Schultz and his colleagues at Berkeley and LBNL first showed 2 years ago that the idea wasn't farfetched when they applied combinatorial techniques to synthesize a collection, or library, of 128 different superconducting compounds (*Science*, 23 June 1995, p. 1738). None of them beat the industry leaders, but the proof of principle caught people's attention. Since then, they and others have made libraries of catalysts, semiconductors, light-emitting phosphors, polymers, and magnetic materials.

In all these efforts the strategy is essentially the same: to use robots and other automation devices to rapidly synthesize and screen the activity of different compounds. With the superconductors, for example, Schultz and his colleagues used a series of masks to pattern the deposition of seven different oxides—each made up of oxygen bound to one or two other elements—creating a gridlike array in which each 1 × 2 millimeter rectangle contained a different combination of elements.

Most of these early efforts have turned out relatively small libraries, containing tens or hundreds of different materials. But at the April Materials Research Society meeting in San Francisco, Wu and several Symyx colleagues reported picking up the pace, creating a library of 26,000 different inorganic phosphors—compounds that make up the heart of televisions and desktop computer displays because they emit light when zapped with electrons. At the same meeting, LBNL's Xiao-Dong Xiang reported making a similar, but smaller, library, which he also described in the 23 June issue of *Applied Physics Letters*. These are eye-catching efforts, because researchers around the globe are working frantically to create phosphors for flat-screen displays. They will have to emit light with less energy input than current phosphors because electrons can't accelerate to the same speed in the thinner displays.

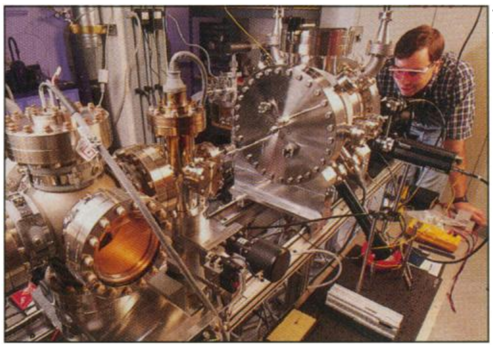
Wu and Henry Weinberg, a physical chemist and Symyx's chief technical officer, say their team's initial screens turned up one red-emitting and one blue-emitting phosphor that are as good as or better than those already on the market, although the researchers declined to give further details until they have patented and published their finds. Xiang says his team's screens also turned up several promising phosphors that appear to be more efficient and stable than those found in products today.

Phosphors, says Weinberg, are an obvious early application of the combinatorial approach to materials science, because the new compounds can be screened simply by shining ultraviolet light on them and seeing which ones shine brightest. At this point, however, the hottest commercial prospect for combinatorial materials may be the production of new catalysts. The reason, says Bob Ezzell, a chemist at The Dow Chemical Co. in Midland, Michigan, is that catalysts are ubiquitous in industrial processing, and a compound that performs new reactions or accomplishes old ones more efficiently "can revolutionize whole areas of chemistry."

Until now, finding that magic catalyst has been a tedious process in which researchers strive to understand exactly how the reactions take place so that they can design new catalysts to carry out just the reaction they want. Even when they have a basic idea of what they are looking for, researchers still face a bewildering array of possibilities. Take the class of catalysts known as homogeneous catalysts. These compounds typically consist of a central metal atom connected to organic arms that surround the metal and ensure that it reacts with only the compounds of interest. The chemical makeup of the arms, and therefore the selectivity of the catalyst, can come in untold variations.

That makes the numbers game an attractive alternative to rational design. "The idea isn't to give up rational design," says Tom Baker, a combinatorial catalyst developer at Los Alamos. Rather, the idea is to use it to figure out which kinds of catalysts have a better shot of working, then create a library of such materials in hopes that one or more will turn out to have catalytic activity.

Such efforts are already beginning to show promise. Last year, for example, Amir Hoveyda and his colleagues at Boston University reported in the 18 August issue of *Angewandte Chemie, International Edition in English* that they had used combinatorial techniques to discover a new catalyst capable of selectively creating single chiral compounds—members of molecular twins that are mirror images of each other—which are useful in synthesizing new drug molecules. "That was a landmark paper," says Mark Scialdone, a combinatorial chemist at DuPont Central Research and Development Experimental Station in Wilmington, Delaware. "It's getting people to believe that combinatorial chemistry can be useful for finding new catalysts as well as drugs."



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Not so fast

Tempering the enthusiasm, however, is a series of knotty scientific problems that confront the new technology. For one, unlike drugs, tiny samples of materials can behave very differently from large bulk quantities that are used in the real world, says Donald Murphy, who heads the applied materials research division at Lucent Technologies' Bell Labs in Murray Hill, New Jersey. And even if you manage to create a promising thin film in a 200 × 200 micrometer patch, there's no guarantee that it can be produced in the bulk quantities needed commercially.

Other key problems include testing the activity of microscopic amounts of hundreds or thousands of new compounds simultaneously. Few materials assays have been adapted for arrays generated by combinatorial methods. Until they are, says Ezzell, there's little point in going to the trouble of high-speed synthesis if you can't screen the results rapidly.

Rapidly analyzing the materials in a combinatorial grid to tell what's been created is also a potential stumbling block. Even if researchers know what elements they have added into a promising new phosphor, for example, they have no idea whether the elements have mixed evenly or remained segregated, which means that they don't know the exact structure of the resulting material.

Wu says these concerns are valid, but he notes that researchers at Symyx and elsewhere are working to develop many of the screens and characterization schemes to work on arrays of compounds all at once. Xiang and his LBNL colleagues, for example, are finishing work on a pair of new microscopes that will be able to assay the electronic and magnetic properties of between 1000 and 5000 superconducting samples a day. Schultz adds that whatever the hurdles in scaling up production from a tiny sample to a useful amount of product, combinatorial techniques speed up the time-consuming front end of the discovery process, identifying promising compounds for further testing and development.

But even if the technical problems can be solved, there's yet another barrier to be overcome: money. Symyx is spending millions of dollars on robotic synthesis and screening machines, computerized databases, and an array of experts to carry out all the synthesis, characterization, and informatics tasks involved. At the same time, "there's not quite as much of an economic driving force" for new materials as there is for new drugs, says DARPA's Dubois. This combination of high start-up costs and uncertain returns has left many company research directors feeling torn. "It's a very interesting and intriguing approach," says chemist Gerald Koermer of Engelhard Corp. in Iselin, New Jersey. However, he adds, "most research managers with budget responsibilities don't want to take too big of a gamble" on an unproven technology. "Their tendency is to hold back until the odds get better."

As a result, most companies are hedging their bets. DuPont researchers, for example, established a combinatorial chemistry effort to work on developing new agrochemicals 3 years ago. So they were able to put their in-house machinery and expertise to work in a small, exploratory combinatorial materials effort. Hoechst is using its deal with Symyx to buy access to the technology without having to establish its own effort, a model also being explored by officials at Dow and Engelhard. Such deals represent "a relatively small amount of the overall research budget" for industrial giants, says Zaffaroni. And if the venture doesn't pan out, the big companies can walk away without disbanding an internal effort.

Of course, Zaffaroni and other true believers are confident that won't happen. And if their optimism about the new technology is justified, says Ezzell, "there will be a lot of people in this sandpile before all is said and done."

–Robert F. Service