

Combinatorial Materials Synthesis

FEATURE

by Jennifer Ouellette

This technique allows simultaneous creation of numerous diverse new compounds

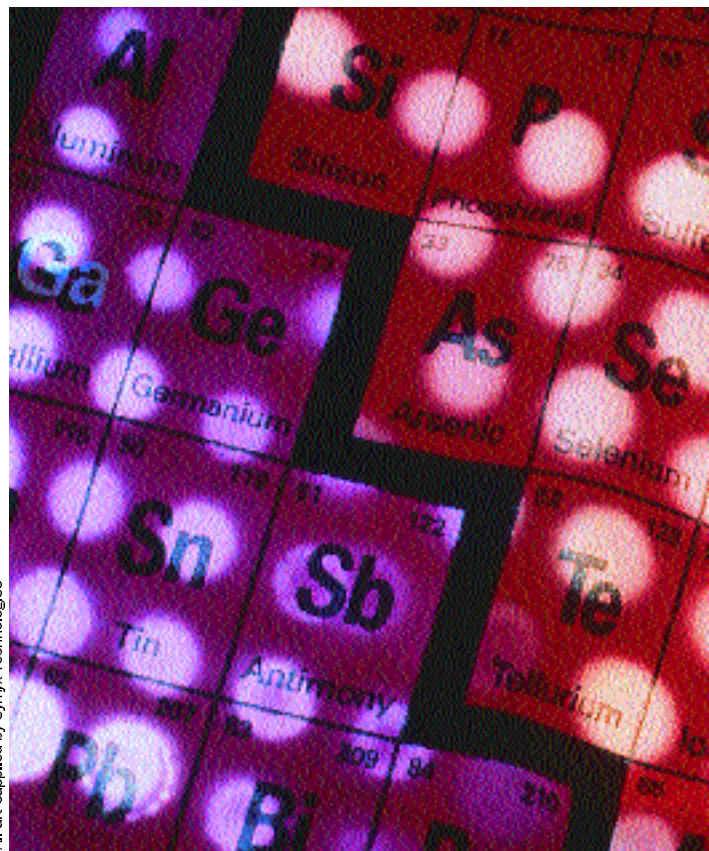
Over the last decade, combinatorial chemistry has revolutionized the pharmaceutical industry's discovery of new compounds and permanently altered the drug-development process. Now, materials scientists are applying the same approach to accelerate the discovery of other new compounds, a move that some believe could dramatically alter the existing paradigm for discovering and commercializing new materials. The current focus is on high- T_c superconductors, luminescent materials, giant magnetoresistive compounds, dielectric and ferroelectric materials, catalysts, and polymers—all materials with promising industrial applications.

Accelerating the discovery rate for new compounds is critical to maintaining U.S. competitiveness in materials science, according to a recent report by the National Academy of Science's Committee on Science, Engineering and Public Policy. The panel found that although the United States currently leads the world in biomaterials and metals research, its leadership in developing electronic-photonic materials is endangered by cutbacks in exploratory industrial research. Moreover, the United States, which once dominated the development and commercialization of magnetic materials, now shares this leadership with Europe and Japan.

The panel singled out materials synthesis and processing—specifically of composites, catalysts, polymers, and biomaterials—as particularly weak in the United States, while in Europe and Japan these areas have a high priority. "Thorough research can take time, and bringing a new material into the marketplace can take more time," the panel concluded. "The short-term focus of the U.S. innovation system presents the danger of blocking the development of important materials concepts."

Hence the growing interest in combinatorial chemistry. This discovery method allows researchers to synthesize large numbers of structurally diverse compounds by assembling all possible combinations of smaller subunits, or "building blocks," according to Mark Gallop, senior director of combinatorial chemistry at Affymax Research Institute (Palo Alto, CA), a company that pioneered the use of the technique for drug discovery. Combinatorial chemistry differs from the traditional discovery method, in which researchers attempt to predict beforehand the most likely molecular structures that will yield the desired properties. The new approach, in con-

trast, relies on creating large numbers of candidate compounds and screening them to discover which one offers the best solution for a specific need. It can dramatically accelerate the discovery and optimization process.



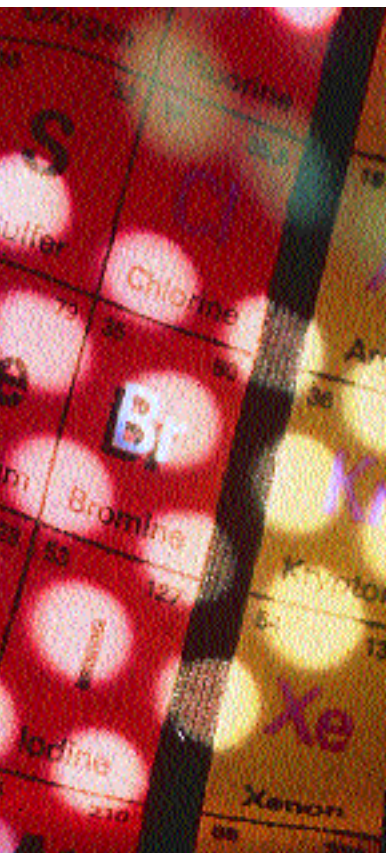
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Birth of a method

The combinatorial method has its roots in nature, specifically the mechanisms used by the immune system to select antibodies to combat invading agents. The human body boasts a "library" of about 1 trillion differently shaped antibodies, each consisting of different combinations of protein chains. When faced with a virus, for example, the immune system scans its library and selects the antibodies that will best bind to and battle the virus. "There is no rational design of antibodies to fit a particular virus," says Peter G. Schultz, a chemist at Lawrence Berkeley National Laboratory (LBNL). Schultz first used a combinatorial approach in the late 1980s to invent catalytic antibodies, which, because of their shape, promote certain chemical reactions.

Affymax, founded in 1989 by Schultz and Alexander

Zaffaroni, was the first commercial company to apply combinatorial methods to drug discovery. Over the last five years, combinatorial strategies have attracted hundreds of millions of dollars into biotechnology and pharmaceutical companies.



The approach is also finding application in DNA synthesis and genetic analysis (see *The Industrial Physicist*, 9/98, p. 12).

These developments have helped set the stage for combinatorial materials synthesis. Schultz was the first to apply the combinatorial approach to materials synthesis in 1995, working with his LBNL colleague Xiao-Dong Xiang. Most new materials with interesting physical properties, such as high- T_c superconductivity or giant magnetoresistance, consist of several different elements. This complexity makes it extremely difficult to discover new materials; current methods yield

useful new compounds at a rate of approximately one per day. "When a material is composed of multiple components, theory provides little guidance [to predicting the new compound's properties,] and the number of possible combinations could easily take one scientist a lifetime to prepare and analyze," says Isy Goldwasser, president of Symyx Technologies (Santa Clara, CA), a start-up venture that is pioneering the commercialization of combinatorial methods for materials synthesis.

In fact, the five elements in column V of the periodic table represent millions of potential compounds because metals can be combined at different ratios and form different molecular structures, depending on temperature or pressure. "In the vast majority of cases, the important discoveries in materials science are serendipitous," says Xiang. "It is very difficult to predict how these complex

structures will behave before you make them." By using a combinatorial strategy, researchers can investigate many atom substitutions and ratio adjustments in a single combinatorial library.

Commercialization

The cornerstone of combinatorial materials synthesis is thin-film technology, which enables rapid manufacture of tiny amounts of complex metals layered onto a substrate and heated to mix the elements and create a stable compound. "Application of combinatorial chemistry to making libraries of solid-state thin films is of particular current interest because so much of modern electronics is thin-film based," says Eric Isaacs, a scientist at Bell Labs/Lucent Technologies (Murray Hill, NJ), and a member of the LBNL collaborative effort. "In such libraries, each member can be individually addressed by adaptations of standard characterization techniques, such as transport or photoluminescence, potentially making trial-and-error discovery of new materials very efficient."

Schultz and Xiang developed a method of sputtering through masks to deposit thousands of distinct combinations of metal-oxide molecules onto an area the size of a square on a checkerboard, creating the first combinatorial library of advanced materials. According to Gabriel Aepli of NEC Research Institute (Princeton, NJ), another collaborator with LBNL, a primary mask is used to lay down a grid of separate squares. A secondary mask, laid atop the primary mask, blocks out specific portions of the rows and columns of the grid. By sending the metals through different secondary masks, each metal can be deposited on particular sections of the grid. The resulting materials are then scanned for interesting electrical properties.

The technique was first tested on a small 16-member library of high- T_c superconductors, and was later expanded to 128-member libraries with combinations of seven metals. By November 1995, Schultz and Xiang had used combinatorial libraries to discover new giant magnetoresistive compounds having complex ratios of four to six atoms. In a magnetic field, the electrical conductivity of these metal crystals changes, and they lose as much as 72% to 99.9% of their resistance. Such materials greatly interest the electronics industry as candidates for the next generation of magnetic recording heads.

In 1996, Schultz and Zaffaroni formed Symyx, which—in collaboration with industrial partners such as Bell Labs/Lucent Technologies and NEC—is merging miniaturization, automation, and parallel-processing

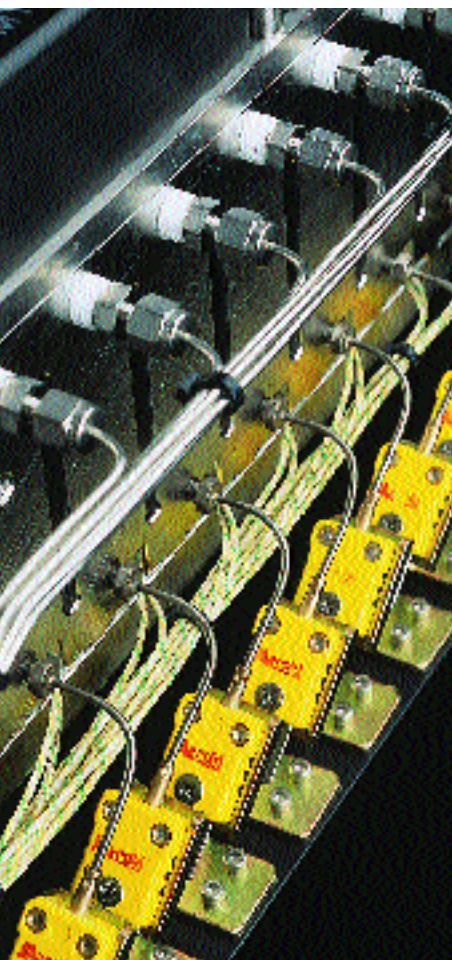


Figure 1. Control system for parallel reactors that are used for synthesis and screening.

technologies with chemistry to generate and evaluate diverse libraries of 100 to 100,000 different materials. Symyx's current focus is on nascent commercial opportunities in the chemical and electronics industries. The latter effort targets the discovery of new solid-state compounds and determining how well certain materials fit into integrated systems in a device. "By next year, our goal is to have made and screened 1 million materials across electronics, catalysis, and polymer science, and we hope to have several breakthroughs in terms of discovering new materials as a result," says Goldwasser.

As part of its broader commercialization strategy, Symyx has formed key research collaborations with four chemical-industry giants. In February 1997, Hoechst AG committed to a five-year, \$43 million research collaboration for the discovery and development of new materials, especially catalysts and polymers for both high-volume commodity chemicals and life-science applications. Symyx also signed a \$53.1 million research collaboration agreement with Bayer AG (Leverkusen, Germany) in March of this year, focusing on new catalysts, polymers, and electronics materials. In addition, Bayer Innovation, a corporate venture fund of Bayer AG that invests in innovative high-tech companies, has made an initial equity investment of \$5 million in Symyx.

In April, Ciba Specialty Chemicals announced a two-year research collaboration with Symyx to use combinatorial strategies to discover new pigments for plastics, coatings, fibers, fabrics, and other products. A fourth research collaboration with BF Goodrich was announced in October. It will develop new catalysts and polymers used in the production of high-performance materials. Other major companies are setting up in-house facilities for combinatorial materials synthesis, including Kodak, Dow, Englehard, DuPont, BASF, and General Electric.

Equipment manufacturers are also developing products for this emerging market. Kurt J. Lesker Co., a leading manufacturer of vacuum components and systems, recently introduced a new system with six sputter sources to generate multicomponent thin films or superlattices with interleaving layers of magnetic, conductor, semiconductor, insulator, and optically active materials. According to company spokesman Mike McKeown, its complete computer control of substrate selection and

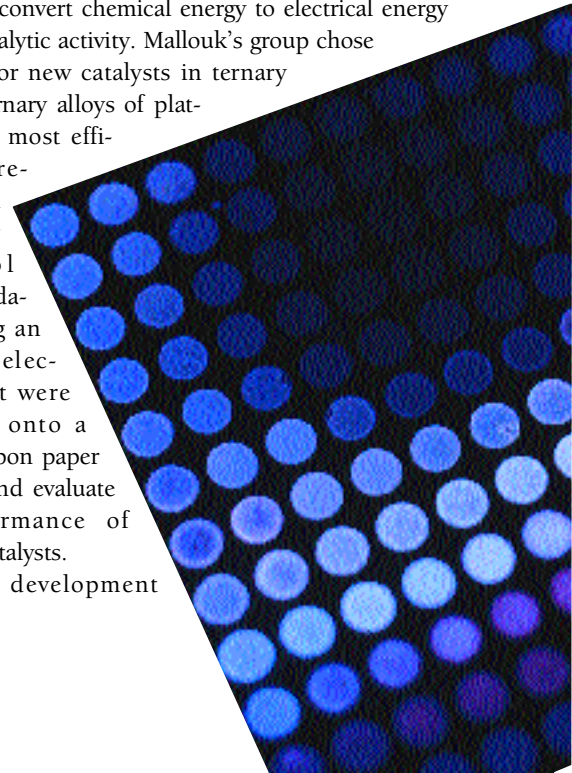
temperature, deposition power and shutter movement, mask movement, and even direction of the magnetic field bathing the substrate, is ideally suited to combinatorial investigations of alloys, superlattices, and giant magnetoresistive materials.

Applications

Symyx scientists quickly validated their approach in 1997 by synthesizing and screening more than 25,000 different luminescent materials in a search for new phosphors for advanced display technologies. The choice of phosphor material is a key factor in the future of field-emission displays, according to Charles Hunt of the University of California, Davis, who is using combinatorial techniques to optimize the properties of new refractory metal-oxide phosphors. "The proper phosphors must reproduce the natural color gamut, complete with currents and voltages accessible in a flat-panel display, and be compatible with a field-emitter array," he says. "Empirical methods did not deliver efficient phosphors for such an application." In contrast, the phosphors Hunt has created using a combinatorial approach have proved comparable to or better than standard industrial phosphors.

Combinatorial synthesis is also useful in the discovery of new homogeneous and heterogeneous catalysts. Thomas Mallouk, director of Pennsylvania State University's Center for Miscellaneous Chemistry, uses such methods to discover better electrocatalysts for fuel-cell applications. Fuel cells offer the potential for better fuel efficiency than combustion engines because they are able to convert chemical energy to electrical energy through catalytic activity. Mallouk's group chose to search for new catalysts in ternary and quaternary alloys of platinum—the most efficient pure-metal catalyst for methanol electro-oxidation—using an array of electrodes that were deposited onto a strip of carbon paper to screen and evaluate the performance of potential catalysts.

Polymer development



could also benefit from combinatorial discovery. In addition to their established consumer markets in the chemical industry, polymers are proving useful as sensing materials. David R. Walt, a chemical engineer at Tufts

University, has incorporated an array of fluorescent-based polymer sensors into a device, known as an “electronic nose,” to identify pathogens in food products or detect substances such as illicit drugs or explosives. Nathan Lewis of the California Institute of Technology has developed a similar device using sensors based on electrical conductance. The devices adopt a somewhat combinatorial approach because they use cross-reactivity, in which a user analyzes the pattern generated from all the sensors rather than looking at each individual sensor’s response. Walt’s group also uses combinatorial synthesis to identify new polymer sensing materials, using four discrete combinations of two monomers to achieve a surprising degree of diversity.

Challenges

Despite the enormous advantages of applying combinatorial strategies to materials discovery, the approach does have limitations. For now, application is only feasible where the physical properties of interest can be conveniently measured, and where the chemical properties of the materials being synthesized yield to thin-film preparation.

Moreover, many of the new materials discovered to date are not purely synthesized into a single phase. This is a common problem in materials science when thin-film sputtering is used and is not unique to combinatorial synthesis. “Even with a single large piece of material, getting it into a single phase is not trivial,” says Isaacs. “And now you have 10,000 thin-film materials on a single

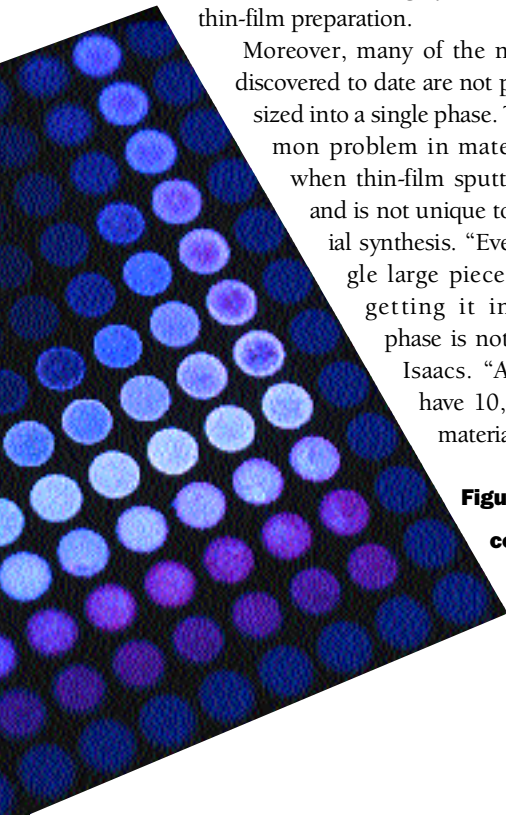


Figure 2. Typical combinatorial material library.

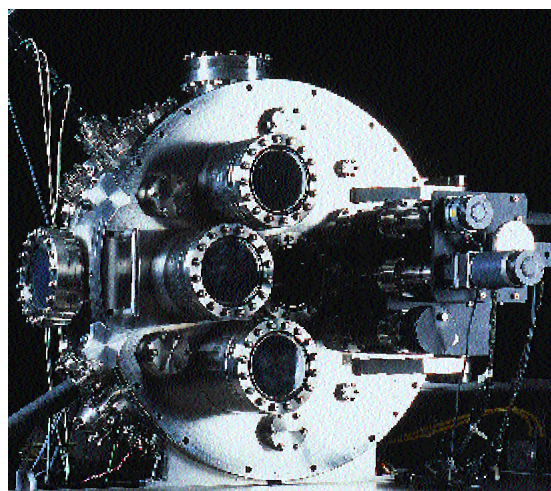


Figure 3. Pulsed laser deposition robot creates libraries of combinatorial materials by laying down successive thin layers of different materials.

wafer, each crying out for slightly different processing. Those challenges need to be overcome to really make the technique pay off by achieving 10,000 high-quality solid-state materials on a single wafer.” Xiang and his collaborators

have recently demonstrated the capability to fabricate pure, single-phase, high-quality epitaxial materials in combinatorial libraries in the laboratory, a significant advance in overcoming this challenge. However, the problem of scaling up the process for bulk manufacture of such materials on a production line remains great.

Better, more-rapid characterization methods are also needed to screen and analyze the large libraries of compounds for specific properties. Schultz and Xiang have used a novel scanning-tip microwave near-field microscope to characterize the microwave properties of a high-density combinatorial thin-film library of doped ferroelectric materials. A collaboration between Washington State University and IBM’s T. J. Watson Research Center used positron annihilation spectroscopy depth profiling to nondestructively probe thin dielectric films, while researchers at the National Institute of Standards and Technology in Boulder, Colorado, recently applied a new microwave wafer-probing technique.

Isaacs favors his synchrotron-based X-ray microprobe to directly characterize individual films of combinatorial libraries. “While analogous techniques employing other probes are very useful, X-rays are unique because their penetrating power allows characterization both nondestructively and under arbitrary environmental conditions,” he says. “The bottom line is that you need X-rays to look at any new material.” His team hopes to eventually develop arrays of X-ray microbeams suitable for rapid characterization.

For some researchers, combinatorial synthesis is not so much a radical departure as a natural progression from traditional methods of synthesis. “Materials scientists have always put different materials together into compounds,” says Aeppli. “It’s just that now we’re able to do it on a much larger scale because of technological advances. I think in 10 years, everyone will be doing materials discovery this way.”

Xiang, however, sees progress occurring more slowly, particularly in the area of electronics materials. “When all of the scientific community in the materials-research area adopts the concept and practices in their research, then the real change may come,” he says. 