

Combinatorial solid-state chemistry of inorganic materials

Throughout history, scientists and engineers have relied on the slow and serendipitous trial-and-error process for discovering and developing new materials. In contrast, an emerging theme in modern materials science is the notion of intelligent design of materials. Pioneered by the pharmaceutical industry and adapted for the purposes of materials science and engineering, the combinatorial approach represents a watershed in the process of accelerated discovery, development and optimization of materials. To survey large compositional landscapes rapidly, thousands of compositionally varying samples may be synthesized, processed and screened in a single experiment. Recent developments have been aided by innovative rapid characterization tools, and by advanced materials synthesis techniques such as laser molecular beam epitaxy which can be used to perform parallel-processed design and control of materials down to the atomic scale. Here we review the fast-growing field of combinatorial materials science, with an emphasis on inorganic functional materials.

HIDEOMI KOINUMA¹ AND ICHIRO TAKEUCHI^{2*}

¹Materials and Structures Laboratory, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan

²Department of Materials Science and Engineering, and Center for Superconductivity Research, University of Maryland, College Park, Maryland 20742, USA

*e-mail: takeuchi@squid.umd.edu

The practice of materials synthesis is analogous to cooking in the sense that many factors — such as raw materials, tools and recipes — must be carefully selected and optimized by ‘tasting’ at various stages. The conventional one-by-one method for arriving at a good product takes a lot of time and energy. To compete successfully and claim priority with new products and recipes, one must be able to accelerate the pace of the optimization process. Component miniaturization and integration have played key roles in technological innovation, and they have led to breakthroughs in the electronics industry. In the past two decades, the pharmaceutical and DNA-sequencing industries have witnessed the emergence of similar innovation in the form of combinatorial chemistry and high-throughput screening (see, for example, ref. 1). These techniques are now being extended to the field of materials science and engineering^{2–4}.

In the combinatorial approach, a large number of compounds with different compositions are synthesized and characterized together in parallel.

The scope of the approach is far-reaching, and it can be used to address materials issues at different levels in a wide spectrum of topics ranging from catalytic powders^{5,6} and polymers⁷ to electronic and biofunctional materials. In solid-state applications, the concept and effectiveness of the approach have been demonstrated by successful discoveries of new compounds in key technological areas including optical, dielectric and magnetic materials^{4,8,9}.

Although the roots of this approach can be traced back to early phase-mapping experiments^{10–13} in the 1960s, recent developments were spearheaded by work at the Lawrence Berkeley National Laboratory in the 1990s¹⁴. In addition to serving the immediate materials needs of industry, combinatorial techniques can be used to tackle fundamental issues of materials physics and chemistry. Composition spread and phase-diagram mapping experiments (where an entire compositional phase diagram is mapped onto a single chip) have proved to be highly effective in rapidly uncovering and delineating the complex composition–structure–property relationships of unknown materials systems.

Thin-film synthesis techniques incorporating spatially varying or selective deposition can be used to create combinatorial libraries and composition spreads. There have been great developments in this area, and tools for lattice engineering at the subnanometre level, such as laser molecular beam epitaxy (LMBE), have been used to fabricate compositionally varying samples¹⁵. In particular, techniques using controlled molecular-layer deposition to fabricate thin-film and junction device

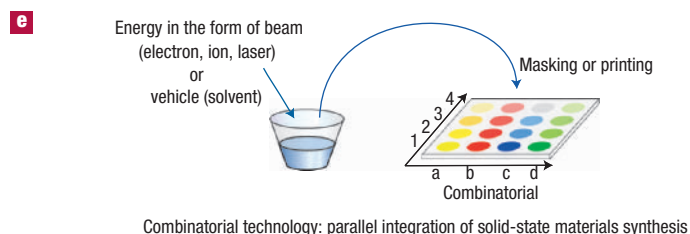
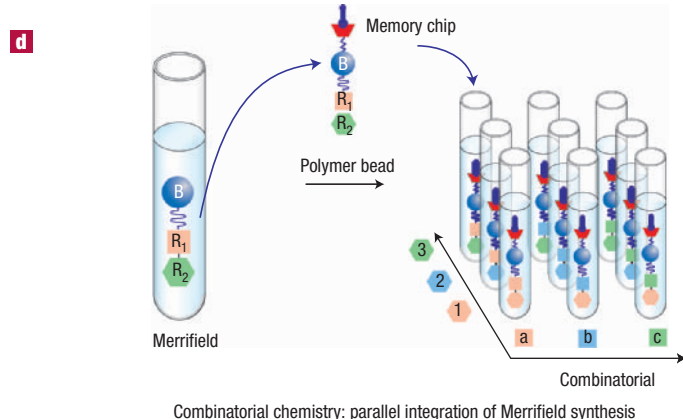
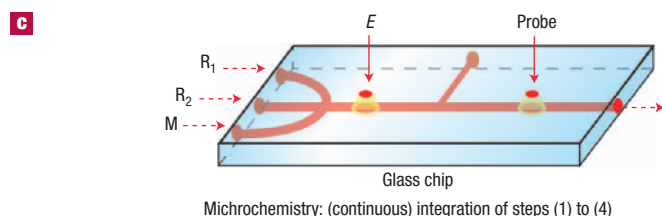
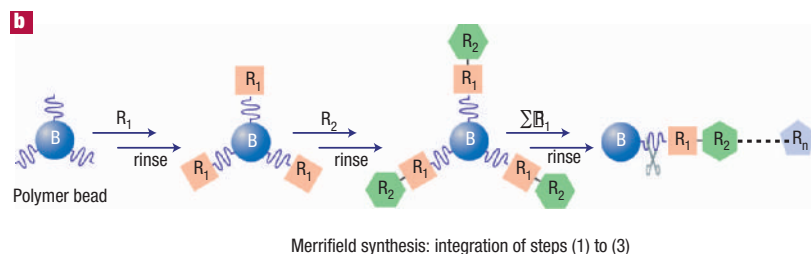
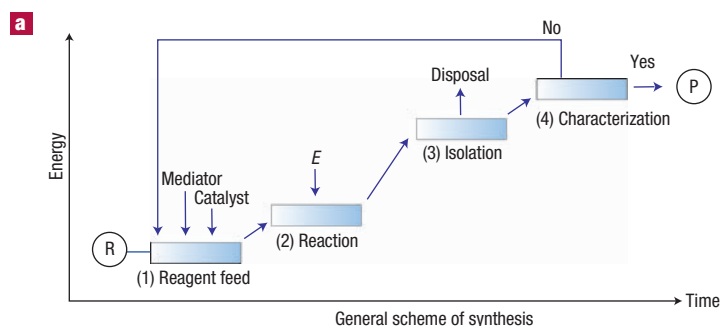


Figure 1 Materials synthesis as a multistep process. **a**, The reaction coordinate of the generalized scheme of materials synthesis where a desired product (P) is obtained from reactants (R). Energy (E) can be supplied in various forms. **b**, Merrifield synthesis can be viewed as a process where steps (1) to (3) in **a** are integrated. Sequences of different reactants (R) are attached to the bead (B). **c**, Microchemistry. Reactants and a medium (M) are mixed in microreactors. Steps (1) to (4) take place in a continuous flow. **d**, Combinatorial chemistry is a parallel integration of Merrifield synthesis. **e**, Combinatorial solid-state technology: solid formation is carried out in parallel in a spatially addressable library.

throughput characterization. Making quick and accurate measurements of a specific physical property from small volumes of materials often represents a considerable feat of instrumentation. Researchers are taking on this challenge, which in some cases has led to the invention of new measurement instruments. A prime example is the scanning microwave microscope, an ideal non-destructive tool for studying ferroelectric, dielectric and conducting materials¹⁸. It is expected that new measurement tools will continue to emerge as important by-products of combinatorial materials research.

EVOLUTION AND INTEGRATION OF SYNTHESIS STEPS

A generalized way of looking at the synthesis of any material is that it follows these steps. (1) Constituents or reactants (R) are simultaneously mixed or sequentially assembled together, often assisted by a medium (M, which can be a carrier gas or a solvent). (2) Energy (E) is supplied to the system using a thermal process or other means of excitation under different conditions (pressure, p , time, t , and so on) so as to drive the reaction process. (3) Desired products (P) are identified and separated from the medium and other by-products formed in the reaction. (4) Finally, the products are characterized: this is the crucial part of any synthesis exercise, and it provides the feedback to the whole cycle. The reaction coordinate of this generalized procedure is schematically illustrated in Fig. 1a. In this manner, the entire product formation process may be considered to be a function of various reaction parameters:

$$P = f(R, t, p, E, M, \dots) \quad (1)$$

In a conventional materials development process, this procedure is performed repeatedly in order to span the input parameter space until a satisfactory product is obtained. In homogeneous organic syntheses involving solvents, step (3) is especially time- and energy-consuming.

In 1963, Merrifield invented a scheme to improve the efficiency of synthesis, which is particularly useful for sequentially bonded compounds^{19,20}. In this technique, reaction sites (linkers) anchored onto resin beads serve as miniature reactors, and they are exposed to an alternating series of reactants and a rinsing solvent (Fig. 1b). This procedure can be viewed as steps (1) to (3) in Fig. 1a integrated as one process. By repeating this procedure, peptides are synthesized from amino acids.

libraries, as well as phase diagram chips, have been developed by Koinuma and colleagues at Tokyo Institute of Technology^{16,17}.

The most formidable task in the combinatorial approach is to implement effective tools for high-

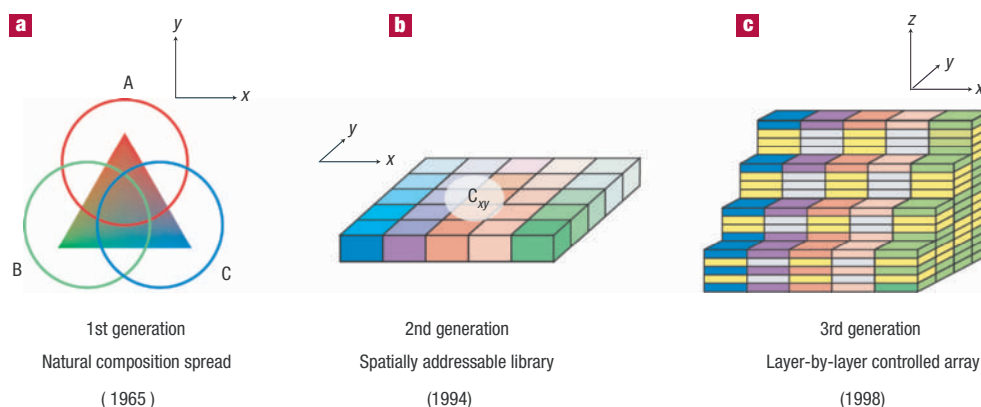


Figure 2 Increasing complexity and evolution in the combinatorial thin-film technology. **a**, The natural composition spread technique was introduced in the 1960s. Varying combinations of three different elements (A, B and C) are obtained at different positions on a wafer. **b**, On a spatially addressable library, each site can be addressed as C_{xy} . **c**, Concurrent atomic layer-by-layer deposition can be used to design an array of crystal structures where stacking of molecular layers is controlled at a nanometre level.

Another embodiment of materials synthesis procedure in which steps (1) to (4) are integrated in series is in the emerging field of microchemistry²¹, where microreactors in the form of trenches patterned on slide glasses are used to carry out homogeneous chemical reactions as well as characterization in a continuous flow of steps (Fig. 1c). A key application of this is a biomedical chip where blood and biosensing agents serve as reactants.

Combinatorial chemistry in essence is a parallel-integrated manifestation of the entire synthesis scheme (Fig. 1d). It has its origin in the parallel processing of the Merrifield synthesis method, which quickly became the common technique in organic synthesis.

The notion of series integration discussed here is rarely applied in inorganic solid-state material syntheses. This is because 'reagents' are usually not carried in a medium (solvent) in inorganic syntheses. Instead of the one-dimensional chemical bond formation in organic and biomolecules, two- and three-dimensional bond formations must be taken into account. The combinatorial synthesis of inorganic materials is best exemplified by a parallel integration of solid formation reactions in the form of spatially addressable arrays of samples (Fig. 1e).

PROGRESS IN COMBINATORIAL INORGANIC MATERIALS SYNTHESIS

The first generation of compositionally varying samples used the composition gradient that occurs naturally across wafers in the thin-film co-deposition process. This had been exploited in composition-spread experiments as early as 1965 (Fig. 2a). Kennedy *et al.* used electron-beam co-evaporation to recreate ternary alloy phase diagrams in individual experiments¹⁰. In fact, they suggested this as a way to replace the conventional metallurgical technique and to perform quick mapping of ternary phase diagrams. Hanak invested substantial effort in developing the composition-spread technique and used it to investigate samples ranging from superconductors and magnetic materials to solar cells and luminescent materials²². Despite some early success, the 'multi-sample at a time' approach did not immediately gain widespread acceptance and use. This was largely due to the lack of

appropriate complementary tools (computers and rapid characterization methods). Equipment available at the time was primitive in measurement and data-handling speed and capabilities.

High-throughput techniques in inorganic materials have re-emerged through direct application of some of the basic concepts of combinatorial biochemistry. In 1994, Xiang and Schultz fabricated spatially addressable 'materials library chips' (Fig. 2b) resembling gene chips and consisting of discrete thin-film samples of cuprate superconductors¹⁴. This can be viewed as the second-generation technique. Subsequently, a general methodology was developed⁸ for systematic synthesis of inorganic materials libraries

Box 1 Materials informatics

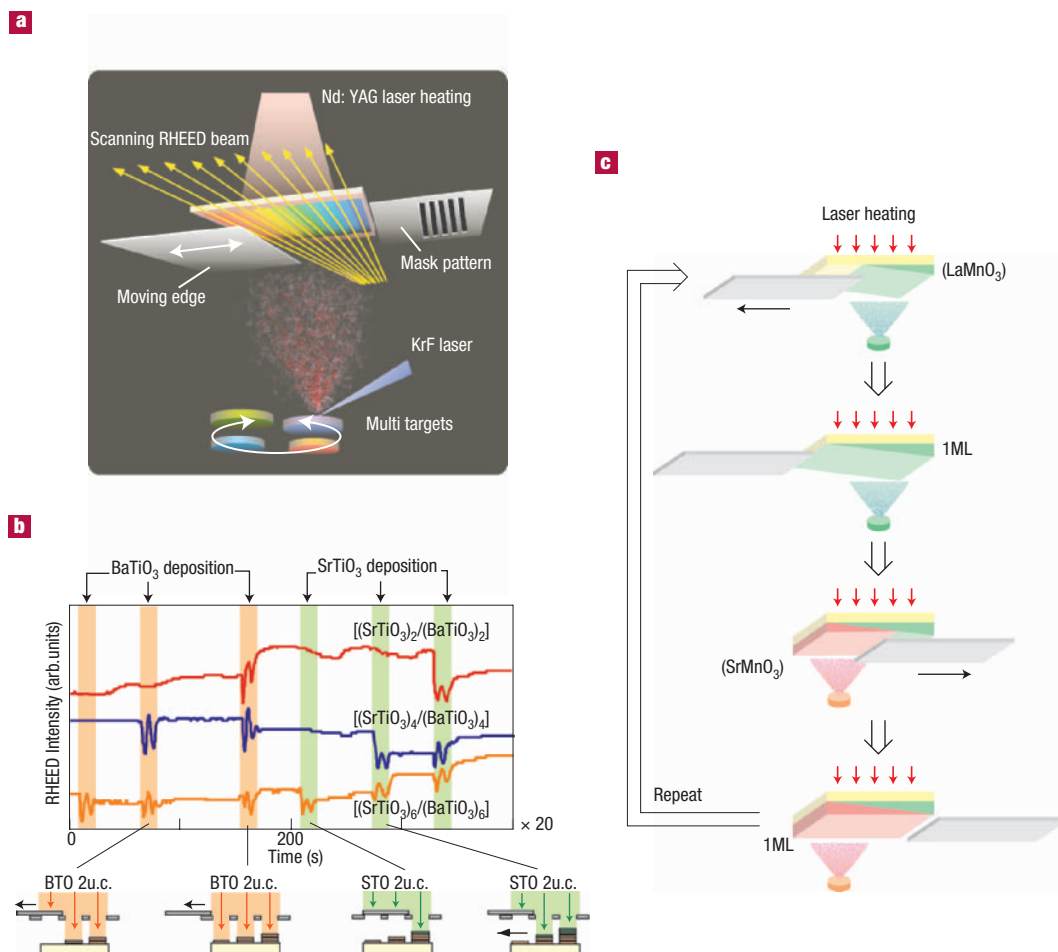
There is a perennial need to efficiently process, analyse and store the enormous amounts of information that stream in and out of combinatorial experiments. Handling a large collection of data through a sequence of experimental steps (design, synthesis and characterization) is a non-trivial feat. This calls for a well-organized data management system, and the daunting task of establishing such systems falls under the emerging field of materials informatics⁶⁹. Its role is to provide a centralized information-based support to the process of materials discovery and establishing new composition–structure–property relationships.

A critical component of materials informatics involves accessing various materials databases. One goal of materials informatics is to link up as many resources as possible so that a large number of databases on known materials are readily available to aid in efficient library design. Cross-referencing various phase-diagram databases (for example, on thermodynamical, chemical reaction and diffusion properties of metals) can help elucidate and delineate the focus of study in ternary composition-spread experiments.

Another crucial aspect of informatics is data mining, where data collected from experiments are examined using various reduction techniques such as principal component analysis in order to extract underlying trends in physical properties, and find new connections between physical parameters. Because combinatorial experiments often represent exploration in multidimensional parameter space, such techniques can play a key role in isolating and identifying 'hidden variables' in experiments. The results could uncover new material behaviour as well as predictions of new compounds⁷⁰. The scope of materials informatics is extensive, but much remains to be developed and fully demonstrated. Its successful use should let us truly harness all the information combinatorial experimentations have to offer.

H.K & I.T.

Figure 3 Combinatorial laser molecular beam epitaxy. **a**, Fabrication scheme of a thin-film materials library. **b**, Reflection high-energy electron diffraction (RHEED) intensities plotted against time, obtained during the simultaneous synthesis of $\text{SrTiO}_3/\text{BaTiO}_3$ (STO/BTO) superlattices on a single library. The layering sequence at different times is schematically illustrated at the bottom. u.c. = unit cell(s). **c**, Synthesis of continuous composition spreads. The shutter is moved back and forth while alternating deposition of two compositions is taking place. Because the thickness of each wedge layer can be tailored to be equal to a monolayer (ML), intimate mixing of the two compositions takes place, resulting in a spread of compositions $A_{1-x}A'_x\text{BO}_3$ where x changes continuously across the chip. Here, $A = \text{Sr}$, $A' = \text{La}$ and $B = \text{Mn}$ (ref. 31).



using a precursor multilayer thin-film technique. Different combinations of amorphous layers (one precursor layer for each element) are put down at different sites, and afterwards materials at different sites are simultaneously thermally processed^{4,8}. Thermal diffusion of amorphous layers and nucleation of phases determine the phase formation in this process.

Although this technique has proved effective in creating diverse compositional variation across libraries, the process is very different from the sequence-controlled synthesis carried out in combinatorial chemistry of organic molecules where bonding of molecules can be sequentially regulated at each site (Fig. 1d). If one were to extend the notion of sequence-controlled synthesis to inorganic synthesis, an atomically controlled layer-by-layer growth of a thin film at each reaction site is necessary. In this manner, one can fabricate a library of artificially designed crystal structures, superlattices or nanostructured devices. Every crystalline material can be viewed as being composed of molecular layers that are stacked periodically. State-of-the-art thin-film deposition techniques such as molecular beam epitaxy and atomic layer epitaxy are used to control atomic layering sequences in thin films. In ceramic thin films, such technologies have seen considerable progress following

the discovery of high-temperature superconductors. Atomic layer controlled deposition of oxides was introduced in 1990^{23,24}, and another breakthrough took place in 1994²⁵ when an atomically finished substrate surface was used for LMBE of SrTiO_3 .

To carry out parallel fabrication of layered structures by atomic layer-by-layer process, combinatorial LMBE (CLMBE) was developed. CLMBE allows concurrent fabrication of a number of artificial lattices or heterojunctions where the composition and thickness of each layer, and the deposition sequence, are manipulated at the atomic scale. This is the third-generation technique, and it represents a considerable improvement in the ability to design new materials systems: libraries can now be constructed where arrangements of atoms are essentially controlled in three dimensions (Fig. 2c).

Three key features of a CLMBE system make it a unique combinatorial synthesis tool: a set of physical masks for defining the film growth site, a scanning reflection high-energy electron diffraction (RHEED) system for *in situ* diagnostics of film growth mode at various sites during the growth, and a fibre-guided Nd-YAG laser for substrate heating (Fig. 3a). By monitoring the growth mode with RHEED and by synchronizing the target switching with mask-layer-movements, synthesis of a number of atomic-layer-

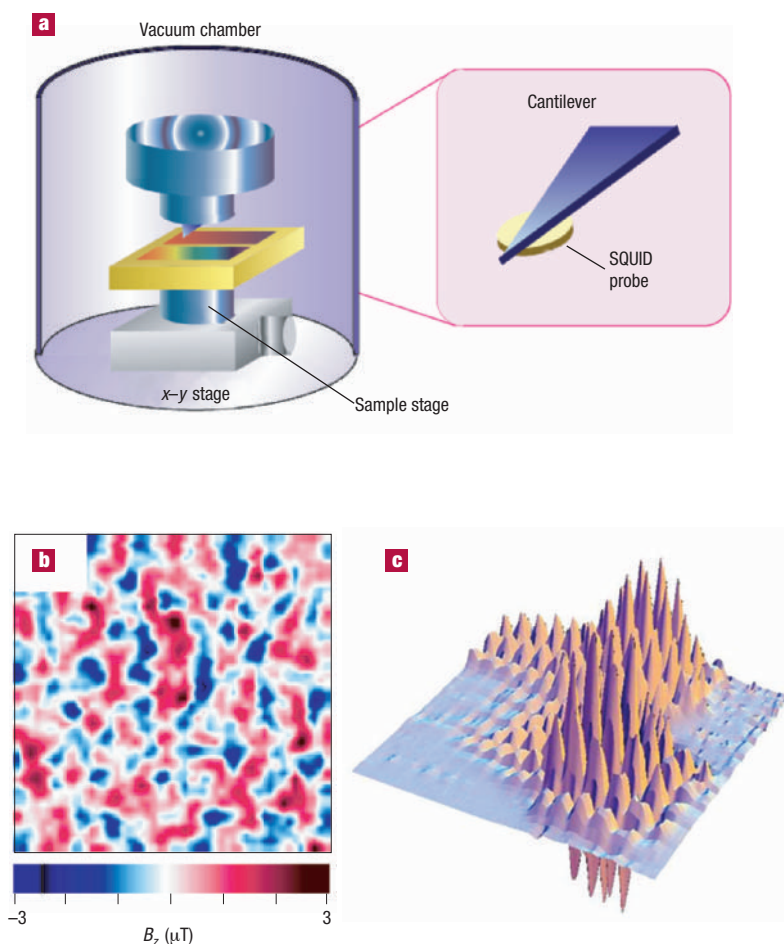
controlled materials can be coordinated on a single substrate. This form of lattice engineering was first verified in simultaneous fabrication of perovskite oxide (ABO_3) superlattices²⁶. In such an experiment, clear intensity oscillation in scanning RHEED, each of which corresponds to the growth of a unit-cell layer, are observed on the surfaces defined by the mask pattern (Fig. 3b). The RHEED beam is scanned across the substrate surface by a pair of coils, and the scanning and image acquisition are synchronized with the moving of shadow deposition masks to control the growth of as many as ten thin-film strips in parallel. The laser, which heats the substrates up to 1,400 °C even in oxygen pressure as high as 1 atm can also be used to create a temperature gradient on a substrate²⁷. Fine-tuning the optimum deposition temperature is a perennial problem in any thin-film research, and this capability allows one to use temperature as a combinatorial parameter. Thus, it is now possible to optimize temperature and composition simultaneously in one experiment. This technique has been successfully used in optimizing dielectric²⁸ and luminescent materials^{29,30}.

In another mode of operation, by automating the motion of the shadow mask during depositions, one can fabricate atomically mixed, epitaxially grown, continuous composition spreads³¹. Figure 3c illustrates this synthesis procedure for composition spread epitaxy of $\text{A}_{1-x}\text{A}'_x\text{BO}_3$ ($0 \leq x \leq 1$). This technique can also be extended to ternary composition spreads^{32,33}.

HIGH-THROUGHPUT CHARACTERIZATION AND SCREENING

In any type of combinatorial investigation, having the correct characterization tool is critical. Without an appropriate high-speed screening technique, high-throughput synthesis serves little purpose. In advanced functional materials, the required performance can be very application-specific. This often translates into having to design, develop and tailor screening techniques that are specialized for individual applications. For instance, capacitor dielectrics in memory devices and tuneable microwave devices using the same class of ferroelectric materials have entirely different sets of performance requirements, necessitating two different screening techniques. The diverse spectrum of functionalities in materials (ranging from gas sensing and optical nonlinearity to piezoelectricity and magnetoresistance) represents a tremendous challenge in high-throughput screening, often requiring new measuring instruments to be developed. This is in contrast to combinatorial chemistry in life sciences, where the luminescent-tagging technique is applicable in a wide range of studies. In many ways, the availability of characterization tools defines the scope of one's combinatorial materials research.

In rapid characterization of thin-film materials, scanning probe microscopy is the order of the day. The ability of the scanning probe microscopes to provide non-destructive, spatially resolved mapping makes them the ideal screening tools for a variety of physical properties. For instance, scanning superconducting quantum interference device (SQUID) microscopes have proved essential for investigation of magnetic materials^{34,35}. Figure 4 shows



the use of scanning SQUID microscopy for combinatorial samples. Microwave microscopes were born out of the need to carry out non-contact electrical impedance measurements, and they are used for quantitative mapping of dielectric or ferroelectric materials libraries as well as resistance or conductance in thin-film libraries and spreads^{18,32,36,37}. Figure 5 shows an example of microwave microscopy of a ternary composition spread³².

Rapid characterization of optical properties (luminescence, transmission and so on) is relatively straightforward because the necessary components for building the measurement setups are mostly commercially available. There are physical parameters that are more difficult to extract accurately from small volumes of (thin-film) samples in libraries, such as thermal conductivity and elastic constants.

Aside from scanning probe techniques, methods that allow screening or detection by visual inspection represent some of the most desirable and elegant embodiments of the combinatorial strategy. Investigation of luminescent materials has yielded some striking examples³⁸, where 'one look' can often convey all the information one initially needs about the distribution of emission profiles. Figure 6 is a luminescent image of a library under ultraviolet excitation.

An important new direction in rapid characterization techniques is the incorporation of

Figure 4 Scanning SQUID microscopy. **a**, Schematic of a low-temperature scanning SQUID microscope. A SQUID probe mounted on a cantilever scans over the sample surface at a cryogenic temperature. **b**, Field distribution image from a part of a $\text{Ti}_{1-x}\text{Co}_{0.2}\text{O}_2$ composition-spread library. The image is $200\ \mu\text{m} \times 200\ \mu\text{m}$, and it was taken at 3 K (ref. 34). **c**, An enhanced scanning SQUID image of a Ni-Mn-Ga composition spread taken with a room-temperature scanning SQUID microscope. The spread was made on a 3 inch wafer, and it was patterned into a square grid. The image covers an area $3\ \text{cm} \times 3\ \text{cm}$. In the ferromagnetic region of the spread, each square acts as its own magnet and gives rise to signals corresponding to positive and negative magnetic field emanating from it³⁵.

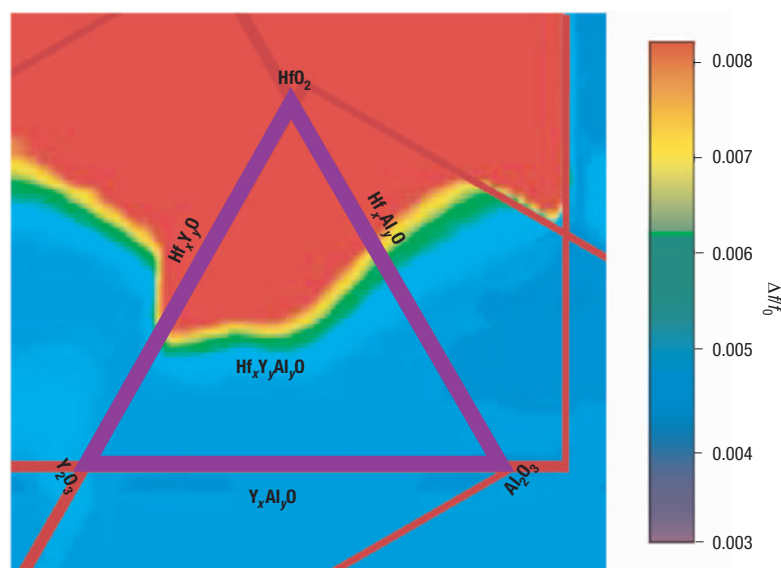


Figure 5 Dielectric mapping of a $\text{HfO}_2\text{-Y}_2\text{O}_3\text{-Al}_2\text{O}_3$ ternary composition spread obtained by a microwave microscope. The composition in the 'phase diagram' is specified by $\text{Hf}_x\text{Y}_y\text{Al}_z\text{O}$ inside the triangle. The three 'side' regions immediately outside the triangle are binary composition spreads, which are $\text{Hf}_x\text{Y}_y\text{O}$, $\text{Hf}_x\text{Al}_x\text{O}$, and $\text{Y}_x\text{Al}_x\text{O}$. The higher frequency shift ($\Delta f/f_0$) corresponds to a larger dielectric constant. The ternary oxide $\text{HfO}_2\text{-Y}_2\text{O}_3\text{-Al}_2\text{O}_3 = 6:1:3$ was found to have a stable amorphous structure while displaying a high dielectric constant³².

microelectromechanical systems (MEMS). Arrays of MEMS devices have a natural configuration that lends itself to high-throughput evaluation of materials performance. For example, arrays of micro-hotplates have been successfully used for developing libraries of inorganic films for gas sensors with individually addressable sensor elements^{39,40} (shown in Fig. 7). Recently, an array of micromachined silicon cantilevers has been used to fabricate a 'self-reporting' library allowing rapid identification of martensitic transformation of shape-memory alloys by visual inspection³⁵. In fact, sensor arrays in general provide a versatile platform for parallel measurements of various chemical and physical parameters that can be efficiently analysed using multiplexed electronics^{41,42}.

Obtaining accurate mapping of composition and phase distribution is essential for constructing the relationship between composition, structure and properties of materials. It is easy to overlook the importance of materials diagnostics in this field. Even when the composition distribution is clearly laid out in the design of a library, the original compositional variation may shift or change during the processing, depending on the synthesis procedure of samples. Materials diagnostics using analytical characterization tools should be an integral part of any combinatorial experiment.

Microprobe techniques are commonly used for spatially resolved elemental analysis. X-ray microdiffraction is a powerful technique for phase mapping^{37,43,44}. In particular, synchrotron techniques can offer unique information about structural (as well as compositional) details of samples with unparalleled sensitivity and spatial resolution⁴⁵. Perhaps the most notable development on the materials diagnostics side is the application of the high-throughput specimen preparation technique for transmission electron microscopy using a focused ion beam (FIB)⁴⁶. This has created a crucial nexus between the traditional materials science of microstructural investigation and the high-throughput approach: it is now possible to select the exact spot on a library to prepare a specimen in several hours for high-resolution transmission electron microscopy. This scheme is illustrated in Fig. 8a.

MATERIALS EXPLORED AND DISCOVERED

Successful uses of the combinatorial approach are rapidly increasing, and the list of compounds discovered continues to grow. Here, we provide some of the recent highlights. Dielectric and ferroelectric materials are important classes of materials used in

Box 2 Limitations of combinatorial techniques

Although there is no shortage of areas where new and improved materials are in demand, not every problem is suitable for the high-throughput methodology. When designing a combinatorial library, it is critical to place a standard reference composition in one corner of the library that can provide the 'reality check' for the experiment. Unfortunately, there are many materials systems where synthesis requires special or exotic processing, and this prevents reliable and reproducible control of composition variation across a combinatorial sample. When one cannot consistently synthesize a standard reference sample, it becomes difficult to make meaningful combinatorial samples. One also has to be careful to avoid a situation where more than the intended parameters are changing across the library. This can seriously complicate the experiment and undermine the interpretation of the results.

There is a trade-off between the diversity one can achieve in a library and the degree of control one has over synthesis of individual samples in the library. For instance, CLMBE can be used to fabricate arrays of structures controlled at the atomic level, but it cannot be used to make hundreds of very different compositions at a time. On the other hand, the precursor technique mentioned above, which does not allow precise control and monitoring of the phase formation, can be used to generate libraries with thousands of discrete compositions.

Although it is convenient to use thin-film techniques to lay out large compositional gradients, the deposition techniques do not necessarily produce equilibrium phases, and mechanical constraints imposed by the substrate could greatly alter the physical properties of interest. When properties of interest are directly associated with microstructural properties such as grain boundary effects, optimizing the properties becomes increasingly challenging. Although one can also systematically vary parameters such as the grain size in a combinatorial way, it is often non-trivial to control such parameters precisely. Finally, we are often reminded of the inherent problem and the intrinsic limit in parallel synthesis of compositionally varying samples: different compositions could have very different optimum process conditions.

All these aspects can conspire in a complex manner to lead to false positives, inaccurate property trends and misses in any combinatorial experiment. Thus, one needs to be able to judge the general applicability of the combinatorial approach and determine the compositional or parameter landscape, which can be rapidly and meaningfully explored on a case by case basis. In the face of advanced synthesis and rapid characterization tools, the fundamental tenet of materials science still rules: insight and deep-rooted knowledge of materials behaviour are the key to a successful experiment.

H.K & I.T.

applications including memory and microwave communication devices. Because the final devices themselves are often in thin-film forms, the results of thin-film libraries are relatively easily transferable to the next stage of materials development. There is an urgent need to develop a new capacitance material to be integrated in the next-generation dynamic random-access memory. Taking the thermal budget of the fabrication process into account, van Dover *et al.* have looked into identifying a new amorphous dielectric metal oxide material with performance better than the amorphous SiO_x used today⁴⁷. Composition spreads produced by off-axis co-sputtering was used to study about 30 multinary phase systems. For each system, synthesis and screening of the spread took about a day, and the 30 systems were investigated in several months. From this work, a 'sweet spot' in compositions on the $\text{ZrO}_2\text{--SnO}_2\text{--TiO}_2$ phase diagram was identified as having optimum properties in dielectric constant and breakdown voltage⁴⁷. The area is centred around $\text{Zr}_{0.2}\text{Sn}_{0.2}\text{Ti}_{0.6}\text{O}_2$ and stretches about 10 at% in each direction. Its synthesis condition was optimized in a standard way, spanning various deposition parameters including pressure and temperature in roughly 30 runs⁴⁸.

For a reasonable chance of finding this composition range by the traditional one-by-one method, one would have had to make about 30 equally distributed compositions to cover each ternary system. This translates immediately to 900 (30×30) bulk target materials, for each of which amorphous films would need to be sputter deposited. Pursuing such a project without a high-throughput strategy is not practical, and it is fair to say that one would not ordinarily even think to look for a new dielectric material in such a way. This example demonstrates how high-throughput experimentation can broaden the scope of one's experiments in general.

Alternatively, one could make 'educated guesses' as to where the best composition might be from known facts about the material system. In the Zn–Sn–Ti–O system, based on microwave properties of known crystalline bulk materials, some amorphous films had been synthesized by others in compositions away from the newly discovered region of the phase diagram. The properties were not good enough to warrant further work, so the sweet spot was missed (R. B. van Dover, personal communication).

The precursor technique has been successfully used to investigate crystalline high- K dielectric materials. A range of compositions $\text{Ba}_{0.12\text{--}0.25}\text{Sr}_{0.35\text{--}0.47}\text{Ca}_{0.32\text{--}0.53}\text{TiO}_3$ was found to display low microwave dielectric loss while maintaining a reasonable dielectric constant³⁶. From dopant library experiments, W-doped $(\text{Ba},\text{Sr})\text{TiO}_3$ was found to show reduced dielectric loss and suppressed d.c. leakage current compared with the undoped host^{49,50}, and these results have been reproduced by other groups⁵¹.

INVESTIGATION OF MAGNETIC MATERIALS

Magnetic materials represent a field in which incremental improvements or new compounds are always being sought for a rich variety of functions, and combinatorial techniques are contributing on several fronts. In the field of spintronics, where the charge and

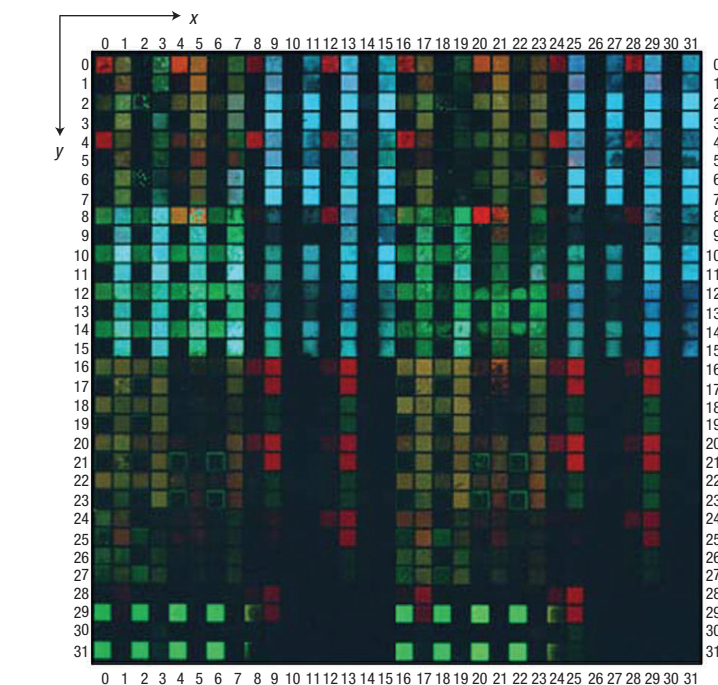


Figure 6 Photograph of a luminescent materials library under irradiation from a multiband emission ultraviolet lamp centred around 254 nm. A quaternary shadow masking strategy was used to create 1,024 different compositions on this library. From this, an efficient blue photoluminescent composite material $\text{Gd}_3\text{Ga}_5\text{O}_{12}/\text{SiO}_2$ was identified³⁸.

spin degrees of freedom of electrons are to be merged for a new paradigm of electronics, the main challenge has been to find suitable magnetic semiconductors^{9,52}. New germanium-based magnetic semiconductors were recently discovered⁵³ by means of combinatorial MBE. The compound $\text{Co}_{0.1}\text{Mn}_{0.02}\text{Ge}_{0.88}$ was found to have transition temperature T_c as high as 280 K and large magnetoresistance effects. The compatibility of this material with silicon makes it a particularly attractive candidate for spintronics.

Composition-spread mapping of ternary alloy systems has uncovered new compositions of ferromagnetic shape-memory alloys³⁵. In the Ni–Mn–Ga system, new ferromagnetic compositions that undergo reversible martensitic transitions above room temperature have been identified in a large Ga-deficient Mn-rich region away from the well-known region of the phase diagram.

The circumstance surrounding the discovery of the transparent oxide ferromagnet is a curious one, and it underscores the significance of serendipity in combinatorial investigation³⁴. The experiment was originally designed to explore new photocatalysts in TiO_2 doped with 3d transition metals (Sc, V, Cr, Mn, Fe, Co, Ni, Cu and Zn). To study systematically the effect of varying dopant amount, Matsumoto *et al.* had made nine different concentration samples for each dopant element on a single substrate, and used two different substrates, LaAlO_3 and Al_2O_3 , to stabilize the anatase and rutile structures of TiO_2 , respectively. Thus, to cover the nine dopant elements, they synthesized a total of 162 ($9 \times 9 \times 2$) different high-quality epitaxial films on 18 substrate chips using CLMBE, over about 3 weeks. This was again a case where without combinatorial synthesis, one would not have thought to pursue such an experiment. Following the synthesis, while the rapid photocatalysis screening tool was still being developed,

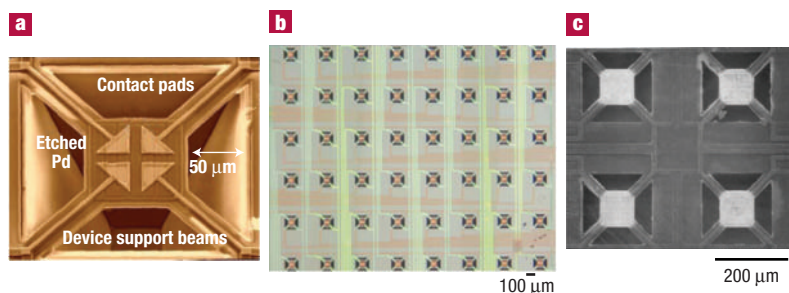


Figure 7 Micro-hotplate device array as a platform for combinatorial study of semiconductor films for gas sensing. **a**, Micrograph of a basic micro-hotplate device. **b**, Micrograph of a 48-element micro-hotplate array showing suspended devices and electrical connection lines. **c**, Micrograph showing the localized deposition of gas-sensing SnO_2 films on a four-element micro-hotplate array accomplished by self-lithographic, thermally activated chemical vapour deposition⁴⁰.

a similar set of libraries containing doped ZnO were being screened for dilute magnetic semiconductors in the laboratory next door. Because TiO_2 itself is a well-known wide-bandgap semiconductor, it was natural also to screen the TiO_2 libraries for magnetic properties using a scanning SQUID microscope. Interestingly, Co-doped anatase TiO_2 showed robust ferromagnetism whereas comparatively little was found in the doped ZnO libraries. Subsequent studies have showed that the magnetism in the Co-doped anatase TiO_2 persists well above room temperature while maintaining its optical transparency and single phase up to the composition of 8% Co.

This discovery has launched a new field of oxide-based dilute magnetic semiconductors, and researchers around the world are now competing to find other oxide materials with similar magnetic properties⁵². Such materials have the potential for exotic future devices where display and memory functionalities are directly integrated. The optimization experiments in this case included detailed studies of composition spreads and varied deposition temperature, and film and

bulk synthesis of individual compositions. The results by Matsumoto *et al.* have been reproduced by many groups around the world using laser ablation and other physical deposition techniques. There are intriguing aspects of the magnetism in this system, and there is currently worldwide effort to understand its origin⁵⁴.

OTHER MATERIALS SYSTEMS

In luminescent materials, the combinatorial strategy has enjoyed much success, partly owing to the simplicity of the initial screening process. For instance, high-quantum-efficiency red-emitting phosphors have been discovered in $(\text{Gd}_{2-x}\text{Zn}_x)_2\text{O}_3:\text{Eu}^{3+}$, which was identified from a library fabricated using an ink-jet liquid dispersion process⁵⁵. Danielson *et al.*⁵⁶ have found a phosphor with an unusual one-dimensional structure, in which a charge-transfer mechanism is the origin of luminescence in Sr_2CeO_4 .

Composition spread experiments can be used to map out the details of known materials systems or probe phase-spaces of previously unexplored materials. There are many examples where they have been used, successfully and rapidly, to construct composition–structure–property relationships^{28,29,31–33,35–37,47,55,57,58}.

Other materials systems whose high-throughput synthesis and screening techniques have been developed include thermoelectric materials and materials for organic light-emitting devices^{59,60}. A combinatorial bulk synthesis technique has been developed for investigation of battery materials, and a new electrode material with a very high electrode potential has been discovered in the Li–Cr–Ti–O system^{61,62}. In the area of glass systems, an automated batch melting apparatus has been developed for high-throughput synthesis, and

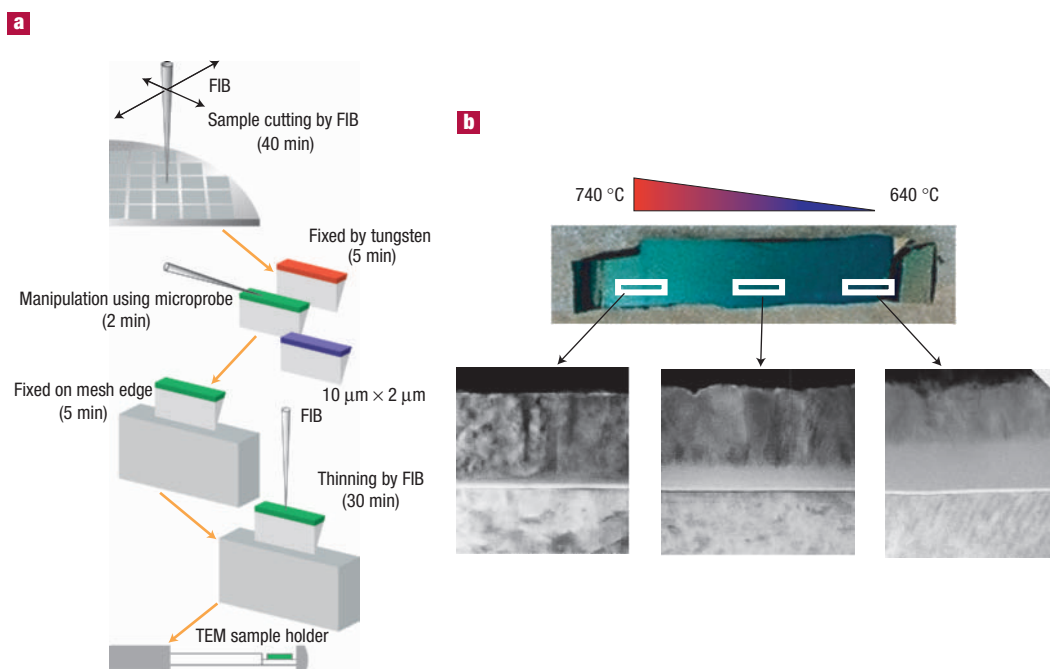


Figure 8 Transmission electron microscopy (TEM) of specific sites of interest on combinatorial samples. **a**, Schematic of rapid TEM specimen preparation process using the focused ion beam (FIB) etching technique. **b**, High-resolution cross-sectional TEM is performed on three selected spots on a gradient temperature library⁴⁶.

new multicoloured glasses with a low transition temperature have been found in the $\text{P}_2\text{O}_5\text{--TeO}_2\text{--ZnO}$ ternary system⁶³.

There is a large community devoted to investigating catalysts and polymeric materials using combinatorial techniques. Unlike functional device materials, materials themselves are commodities in these areas, and significant research efforts are taking place in industry as well as at university and government laboratories. For recent advances in these areas, we refer readers to refs 7 and 64–68.

SUMMARY AND OUTLOOK

Combinatorial and high-throughput methodology promotes deep changes in the practice of materials discovery and development. The notion of search and discover is central to materials science, and the basic idea of high-throughput experimentation can be applied to everything from simple thickness gradient experiments to mapping of multidimensional composition space. In addition to time and cost efficiencies, effective use of the approach translates to enormous environmental savings in resources used for research. By incorporating state-of-the-art materials synthesis techniques such as CLMBE, combinatorial methodology can serve as a tool for intelligent design and tailoring of materials at nanometre scales. One of the most exciting aspects is the ability to bring together disparate ideas and technologies to create a basis for new experimentation. We can continue to expect great advances in synthesis and screening. For instance, incorporation of arrays of active MEMS devices and microfluidic architecture can provide a vehicle for innovative parallel materials processing as well as characterization. Given the diversity of properties shown by solid-state materials, multipurpose characterization tools that can be used in different modes for screening a multitude of functionalities are desirable. Promising new areas on the horizon include combinatorial synthesis of nanoparticles, which are ubiquitous nowadays and have many properties to be optimized. One can also begin to think about inserting the general high-throughput methodology into the materials development process at a point much closer to the end product, for rapid and systematic process engineering. A good example might be in semiconductor manufacturing where a number of process parameters can be quickly optimized at the plant level (J. O. Choo, R. A. Adomaitis, G. W. Rubloff, L. Henn-Lecordier and Y. Liu, manuscript in preparation).

Note added in proof: Recently, a thermal conductivity imaging technique was developed⁷¹, and was demonstrated for diffusion multiple samples.

doi:10.1038/nmat1157

References

- Lebl, M. Parallel personal comments on 'classical' papers in combinatorial chemistry. *J. Comb. Chem.* **1**, 3–24 (1999).
- Takeuchi, I., Newsam, J. M., Wille, L. C., Koinuma, H. & Amis, E. J. (eds) Combinatorial and artificial intelligence methods in materials science. *Mater. Res. Soc. Symp. Proc.* **700** (2002).
- Xiang, X.-D. & Takeuchi, I. (eds) *Combinatorial Materials Synthesis* (Dekker, New York, 2003).
- Takeuchi, I., van Dover, R. B. & Koinuma, H. Combinatorial synthesis and evaluation of functional inorganic materials using thin-film techniques. *Mater.*

Box 3 Combinatorial collaborations

As a testament to its growing popularity, large collaborative efforts and research centres in combinatorial materials science are beginning to appear. Notable ones include the National Institute of Standards and Technology (NIST) Combinatorial Methods Center; the Combinatorial Materials Exploration and Technology (COMET) project, which is a joint effort by the National Institute for Research in Inorganic Materials and the Tokyo Institute of Technology; and the Combinatorial Sciences and Materials Informatics Collaboratory (COSMIC), which is located at Rensselaer Polytechnic Institute, the University of Maryland and the Florida International University, and is supported by the National Science Foundation.

H.K & I.T.

- Res. Soc. Bull.* **27**, 301–308 (2002).
- Jandeleit, B., Turner, H. W., Uno, T., van der Beek, J. A. M. & Weinberg, W. H. *CATTECH* **2**, 101 (1998).
- Senken, S., Krantz, K., Ozturk, S., Zengin, V. & Onal, I. High-throughput testing of heterogeneous catalyst libraries using array microreactors and mass spectrometry. *Angew. Chem. Int. Edn* **38**, 2794–2799 (1999).
- Special issue on combinatorial research and high-throughput experimentation in polymer and materials research. *Macromol. Rapid Commun.* **24**, (2003).
- Xiang, X.-D. Combinatorial materials synthesis and screening: an integrated materials chip approach to discovery and optimization of functional materials. *Annu. Rev. Mater. Sci.* **29**, 149–171 (1999).
- Matsumoto, Y. *et al.* Combinatorial investigation of spintronic materials. *Mater. Res. Soc. Bull.* **28**, 734–739 (2003).
- Kennedy, K., Stefansky, T., Davy, G., Zacky, V. F. & Parker, E. R. Rapid mapping for determining ternary-alloy phase diagrams. *J. Appl. Phys.* **36**, 3808–3810 (1965).
- Miller, N. C. & Shirn, G. A. Co-sputtered Au–SiO₂ cermet films. *Appl. Phys. Lett.* **10**, 86–88 (1967).
- Hanak, J. J., Gittleman, J. I., Pellicane, J. P. & Bozowski, S. The effect of grain size on the superconducting transition temperature of the transition metals. *Phys. Lett.* **30A**, 201–202 (1969).
- Hanak, J. J. The 'multi-sample concept' in materials research: synthesis, compositional analysis and testing of entire multicomponent systems. *J. Mater. Sci.* **5**, 964–971 (1970).
- Xiang, X.-D. *et al.* A combinatorial approach to materials discovery. *Science* **268**, 1738–1740 (1995).
- Koinuma, H. Quantum functional oxides and combinatorial chemistry. *Solid State Ionics* **108**, 1–7 (1998).
- Koinuma, H., Aiye, N. H. & Matsumoto, Y. Combinatorial solid state materials science and technology. *Sci. Technol. Adv. Mater.* **1**, 1–10 (2000).
- Lippmaa, M., Kawasaki, M. & Koinuma, H. in *Combinatorial Materials Synthesis* (eds Xiang, X.-D. & Takeuchi, I.) Ch. 5 (Dekker, New York, 2003).
- Wei, T., Xiang, X.-D., Wallace-Freedman, W. G. & Schultz, P. G. Scanning tip microwave near-field microscope. *Appl. Phys. Lett.* **68**, 3506–3508 (1996).
- Merrifield, R. B. Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* **85**, 2149–2154 (1963).
- Merrifield, R. B. Solid phase peptide synthesis. IV. The synthesis of methionyl-lysyl-bradykinin. *J. Org. Chem.* **29**, 3100–3102 (1964).
- Sato, K., Hibara, A., Tokeshi, M., Hisamoto, H. & Kitamori, T. Integration of chemical and biochemical analysis systems into a glass microchip. *Anal. Sci.* **19**, 15–22 (2003).
- Hanak, J. J. in *Combinatorial Materials Synthesis* (eds Xiang, X.-D. & Takeuchi, I.) eds 7–34 (Dekker, New York, 2003).
- Koinuma, H., Nagata, H., Tsukahara, T., Gonda, S. & Yoshimoto, M. in *Ext. Abstracts 22nd Conf. Solid State Devices and Materials (SSDM 90)* 933–936 (Japanese Society of Applied Physics, Tokyo, 1990).
- Terashima, T. *et al.* Reflection high-energy electron diffraction oscillations during epitaxial growth of high-temperature superconducting oxides. *Phys. Rev. Lett.* **65**, 2684–2687 (1990).
- Kawasaki, M. *et al.* Atomic control of the SrTiO₃ crystal surface. *Science* **266**, 1540–1542 (1994).
- Ohnishi, T. *et al.* Parallel integration and characterization of nanoscaled epitaxial lattices by concurrent molecular layer epitaxy and diffractometry. *Appl. Phys. Lett.* **79**, 1282–1284 (2001).
- Koida, T. *et al.* Temperature-gradient epitaxy under *in situ* growth mode diagnostics by scanning reflection high-energy electron diffraction. *Appl. Phys. Lett.* **80**, 565–567 (2002).

28. Minami, H. *et al.* Rapid synthesis and scanning probe analysis of $\text{Ba}_x\text{Sr}_{1-x}\text{TiO}_3$ composition spread films on a temperature gradient $\text{Si}(100)$ substrate. *Jpn J. Appl. Phys.* **41**, L149–L151 (2002).
29. Kubota, H. *et al.* Combinatorial synthesis and luminescent characteristics of $\text{RECa}_2\text{O}(\text{BO}_3)_3$ epitaxial thin films. *Appl. Surf. Sci.* **223**, 241–244 (2004).
30. Tamura, K. *et al.* Donor-acceptor luminescence in nitrogen-doped ScAlMgO_4 (0001) substrates. *Solid State Commun.* **127**, 265–269 (2003).
31. Fukumura, T. *et al.* Rapid construction of a phase diagram of doped Mott insulators with a composition-spread approach. *Appl. Phys. Lett.* **77**, 3426–3428 (2000).
32. Hasegawa, K. *et al.* Amorphous stability of HfO_2 based ternary and binary composition spread oxide films as alternative gate dielectrics. *Appl. Surf. Sci.* **223**, 229–232 (2004).
33. Takahashi, R. *et al.* Design of combinatorial shadow masks for complete ternary-phase diagramming of solid state materials. *J. Comb. Chem.* **6**, 50–53 (2004).
34. Matsumoto Y. *et al.* Room-temperature ferromagnetism in transparent transition metal-doped titanium dioxide. *Science* **291**, 854–856 (2001).
35. Takeuchi, I. *et al.* Identification of novel compositions of ferromagnetic shape memory alloys using composition spreads. *Nature Mater.* **2**, 180–184 (2003).
36. Chang, H., Takeuchi, I. & Xiang, X.-D. A low-loss composition region identified from a thin-film composition spread of $(\text{Ba}_{1-x}\text{Sr}_x\text{Ca}_y)\text{TiO}_3$. *Appl. Phys. Lett.* **74**, 1165–1167 (1999).
37. Chang, K.-S. *et al.* Multimode quantitative microwave microscopy of *in situ* grown epitaxial $\text{Ba}_{1-x}\text{Sr}_x\text{TiO}_3$ composition spreads. *Appl. Phys. Lett.* **79**, 4411–4413 (2001).
38. Wang, J. *et al.* Identification of a blue photoluminescent composite material from a combinatorial library. *Science* **279**, 1712–1714 (1998).
39. Semancik, S. & Cavicchi, R. E. Kinetically controlled chemical sensing using micromachined structures. *Acc. Chem. Res.* **31**, 279–287 (1998).
40. Semancik, S. in *Combinatorial Materials Synthesis* (eds Xiang, X.-D. & Takeuchi, I.) Ch. 9 (Dekker, New York, 2003).
41. Potyrailo, R. A. & Morris, W. G. Multifunctional sensor system for high-throughput characterization of combinatorially developed materials. *Rev. Sci. Instrum.* **75**, 2177–2186 (2004).
42. Potyrailo, R. A. & Morris, W. G. Parallel high-throughput microanalysis of materials using microfabricated full bridge device arrays. *Appl. Phys. Lett.* **84**, 634–636 (2004).
43. Ohtani, M. *et al.* Concurrent X-ray diffractometer for high throughput structural diagnostics of epitaxial thin films. *Appl. Phys. Lett.* **79**, 3594–3596 (2001).
44. Chang, W. in *Combinatorial Materials Synthesis* (eds Xiang, X.-D. & Takeuchi, I.) Ch. 10 (Dekker, New York, 2003).
45. Issacs, E. D. *et al.* Synchrotron X-ray microbeam diagnostics of combinatorial synthesis. *Appl. Phys. Lett.* **73**, 1820–1822 (1998).
46. Chikyow, T. *et al.* A combinatorial approach in oxide/semiconductor interface research for future electronic devices. *Appl. Surf. Sci.* **189**, 284–291 (2002).
47. van Dover, R. B., Schneemeyer, L. F. & Fleming, R. M. Discovery of a useful thin-film dielectric using a composition-spread approach. *Nature* **392**, 162–164 (1998).
48. van Dover, R. B. & Schneemeyer, L. F. Deposition of uniform Zr-Sn-Ti-O films by on-axis reactive sputtering. *IEEE Electron Device Lett.* **19**, 329–331 (1998).
49. Chang, H. *et al.* Combinatorial synthesis and high throughput evaluation of ferroelectric/dielectric thin film libraries for microwave applications. *Appl. Phys. Lett.* **72**, 2185–2187 (1998).
50. Takeuchi, I. *et al.* Combinatorial synthesis and evaluation of epitaxial ferroelectric device libraries. *Appl. Phys. Lett.* **73**, 894–896 (1998).
51. Chang, W. *et al.* The effect of (Ba, Sr) and $(\text{Mn}, \text{Fe}, \text{W})$ dopants of the microwave properties of $(\text{Ba}, \text{Sr})\text{TiO}_3$ -based thin films. *Mater. Res. Soc. Symp. Proc.* **541**, 699–704 (1999).
52. Chambers, S. A. & Farrow, R. F. C. New possibilities for ferromagnetic semiconductors. *Mater. Res. Soc. Bull.* **28**, 729–733 (2003).
53. Tsui, F. *et al.* Novel germanium-based magnetic semiconductors. *Phys. Rev. Lett.* **91**, 177203–1–4 (2003).
54. Shinde, S. R. *et al.* Co-occurrence of superparamagnetism and anomalous Hall effect in high reduced cobalt doped rutile $\text{TiO}_{2-\delta}$ films. *Phys. Rev. Lett.* (in the press).
55. Sun, X.-D. & Xiang, X.-D. New phosphor $(\text{Gd}_{1-x}\text{Zn}_x)\text{O}_3\text{:Eu}^{2+}$ with high luminescent efficiency and superior chromaticity. *Appl. Phys. Lett.* **72**, 525–527 (1998).
56. Danielson, E. *et al.* A rare-earth phosphor containing one-dimensional chains through combinatorial methods. *Science* **279**, 837–839 (1998).
57. Takeuchi, I. *et al.* Monolithic multichannel UV detector arrays and continuous phase evolution in $\text{Mg}_x\text{Zn}_{1-x}\text{O}$ compositions spreads. *J. Appl. Phys.* **94**, 7336–7340 (2003).
58. Yoo, Y. K. *et al.* *Intermetallics* **9**, 541–545 (2001).
59. Itaka, K. *et al.* High-speed evaluation of thermoelectric materials using multi-channel measurement system. *J. Thermal Anal. Calorimetry* **69**, 1051–1058 (2002).
60. Sun, T. X. & Jabbour, G. E. Combinatorial screening and optimization of luminescent materials and organic light-emitting devices. *Mater. Res. Soc. Bull.* **27**, 309–315 (2002).
61. Yanase, I., Ohtaki, T. & Watanabe, M. Combinatorial study on nano-particle mixture prepared by robot system. *Appl. Surf. Sci.* **189**, 292–299 (2002).
62. Kajiyama, A. *et al.* Synthesis and electrochemical properties of lithium chromium titanium oxide with Ramsdellite structure. *J. Electrochem. Soc.* **150**, A157–A160 (2003).
63. Konishi, T. *et al.* Investigation of glass formation and color properties in the $\text{P}_2\text{O}_5\text{-TeO}_2\text{-ZnO}$ system. *J. Non-Cryst. Solids* **324**, 58–66 (2003).
64. Meredith, J. C., Karim, A. & Amis, E. J. Combinatorial methods for investigations in polymer materials science. *Mater. Res. Soc. Bull.* **27**, 330–336 (2002).
65. Special issue on combinatorial materials research and high-throughput experimentation in polymer and materials research. *Macromol. Rapid Commun.* **25**, (2004).
66. Smotkin, E. S. & Diaz-Morales, R. R. New electrocatalysts by combinatorial methods. *Annu. Rev. Mater. Res.* **33**, 557–579 (2003).
67. Senkan, S. Combinatorial heterogeneous catalysis: a new path in an old field. *Angew. Chem. Int. Edn* **40**, 312–329 (2001).
68. Hendershot, R. J. *et al.* A novel reactor system for high throughput catalyst testing under realistic conditions. *Appl. Catal. A* **254**, 107–120 (2003).
69. Rajan, K. in *Combinatorial Materials Synthesis* (eds Xiang, X.-D. & Takeuchi, I.) Ch. 13 (Dekker, New York, 2003).
70. Suh, C. & Rajan, K. Combinatorial design of semiconductor chemistry for bandgap engineering: ‘virtual’ combinatorial experimentation. *Appl. Surf. Sci.* **223**, 148–158 (2004).
71. Huxtable, S., Cahill, D. G., Fauconnier, V., White, J. O. & Zhao, J.-C. Thermal conductivity imaging at micrometre-scale resolution for combinatorial studies of materials. *Nature Mater.* **3**, 298–301 (2004).

Acknowledgements

We are grateful to many colleagues for collaboration and discussions over the years. We particularly thank the following colleagues for key contributions to some of this work (in alphabetical order): M. A. Aronova, L. A. Bendersky, H. Chang, K.-S. Chang, T. Chikyow, O. O. Famodu, T. Fukumura, C. Gao, T. Hasegawa, S. Inoue, K. Itaka, M. Kawasaki, L. Knauss, M. Lippmaa, S. E. Lofland, T. Makino, Y. Matsumoto, A. Miyamoto, M. Murakami, T. Ohnishi, A. Orozco, G. W. Rubloff, P. G. Schultz, Y. Segawa, S. Todoroki, R. D. Vispute, M. Watanabe, F. C. Wellstood, X.-D. Xiang, T. Yamamoto and Y. Yoo. H.K. acknowledges support from the CREST-JST ‘Combinatorial molecular layer epitaxy’ project (1996–2001) and the COMET project. I.T. acknowledges support from ONR N000140110761, N000140410085, NSF DMR0094265 (CAREER), NSF DMR 0231291 and NSF MRSEC DMR 00-80008.

Correspondence and requests for materials should be addressed to I.T.

Competing financial interests

The authors declare that they have no competing financial interests.