COMBINATORIAL CHEMISTRY

1. Introduction

Thirty-two years ago, J.J. Hanak (1) reported a novel methodology for rapidly screening new electronic materials using thin films composed of two different metal oxides. Hanak demonstrated that, within the constraints of a physical measuring probe, a large number of different compositions could be measured *on a single, small sample*, ie, within the infinitely varying concentration gradient of the two-component mixture. This methodology represented a vastly increased speed for screening new electronic materials, however, a variety of technical and cultural issues precluded broad use until B. van Dover and L. Schneemeyr at Lucent Technologies reported (2) the discovery of new dielectric materials using similar methods as Hanak.

In 1995, a team of researchers at Lawrence Berkeley National Laboratory (LBNL) reported (3) the rapid fabrication of tens, hundreds, and, eventually, tens of thousands in two-dimensional arrays of discrete microscaled samples (pixels) using lithography methods developed for the electronics industry. Importantly, the team developed technologies for the rapid characterization of entire arrays (library) by using a matrix of sensors that corresponded to the samples deposited on the silicon wafer. The researchers commercialized these methodologies, hardware, and software through the start-up firm Symyx Technologies (4) starting in 1997. Symyx developed and marketed "combinatorial methods", or high throughput experimentation (HTE), for advanced materials, and created a new paradigm in materials research for the chemical process industry (CPI) and the advanced materials producers. This discontinuity, or step-change, reflected an earlier response by the pharmaceutical industry toward significant market demands for new products—reduced product innovation cycle time, increased return on research and development (R&D) investment, and industry consolidation. Symyx Technologies facilitated implementation efforts throughout the chemicals and advanced materials industries, with the result that the methodology known as "combinatorial chemistry" is now relatively ubiquitous in companies conducting research in advanced materials, catalysts, and polymers.

Many of the methodologies adopted by advanced materials researchers were developed for drug discovery in the pharmaceuticals industry. Drug discovery had entered the new paradigm of combinatorial chemistry and high throughput screening (HTS) in the 1980s, led independently by Furka (5) and Geysen & co-workers (6). The major industry driver was to develop new therapeutics with very tight time- and cost constraints. Traditional techniques of synthesizing and characterizing synthetic targets one-by-one were too slow. Combinatorial chemists indicated that, in theory, the number of potential drug targets—small organic molecules containing C, H, N, and O atoms —approaches 10^{50}, although the number of compounds considered useful is probably closer to 10^{10}–10^{15} (7), and that the only way to screen this diversity was by using massively parallel synthesis and characterization techniques. A number of review articles have covered these pioneers and subsequent developments (8). The commercial importance, and acceptance, of combinatorial methods became obvious when, in 1994 and 1995, Eli Lilly acquired Sphinx for $80 million, Glaxo plc (now GlaxoSmithKline, GSK) acquired technology leader Affymax for $533 million, and Marion Merrell Dow bought Selectide for $58 million (9). Experimental throughputs using 96-well titre plates were on the order hundreds to thousands of reactions per day (a "hit" in the discovery phase). By 1999, the ability to robotically synthesize and characterize 1 million distinct organic compounds per year was realized by some pharmaceutical companies, driving down R&D costs per sample by two orders of magnitude, to $1 or less per "hit".

Today, many chemical and advanced materials companies have implemented some form of HTE in their discovery research phases, through internal investment, mergers, and acquisitions. The market drivers—global pressures for higher performance specialty materials and higher profits on commodity materials—have pressed these industries to increase productivity in their new product discovery and process development phases. HTE for materials often has little similarity with methods developed in the drug discovery arena, however, researchers have quite effectively leveraged many methods and tools from the pharmaceutical applications (10). This is evident in the area of industrial catalysis, where HTE utilized in the discovery and process development phases have cut concept-to-launch cycle times in half; this represents significant cost savings as well as commercial advantages such as market penetration and intellectual property position.

2. The New Paradigm for Materials Research

2.1. Application Areas.

Many of the market factors that influenced drug discovery are presently driving a need for reducing the cycle time for the discovery and process development of new advanced materials and lower cost chemical products such as pharmaceutical intermediates, fine and specialty chemicals, and commodity chemicals and materials. The transfer of technology from drug discovery has resulted in the development of HTE for inorganic materials, fine and specialty chemicals, and advanced materials. Because HTE techniques are especially suited to complex mixtures containing many different components and/or processing conditions, this methodology lends itself to the discovery of new, higher performance materials that contain multicomponent formulations, for eg, the dopants in electronic materials, or polymer blends in engineering plastics. In addition, HTE permits the screening of compositions that would not otherwise be attempted, ie, it maximizes serendipity. For example, Symyx Technologies Inc. (11) reported the identification of a ternary fuel cell catalyst composition (M-M′-M″) of high selectivity and conversion containing transition metals that show little or no catalytic activity in the three possible binary mixtures (M-M′, M-M″, M′-M″). Broad economic benefits are envisioned from the downstream impact of these methodologies, as indicated in Table 1.

High throughput experimentation (also known as combinatorial methodologies) utilizes synthesis and analysis procedures wherein "libraries" of many tens, hundreds, or thousands of discrete samples are fabricated, processed, and characterized in parallel in hours and days, rather than the months and years, at a fraction of the cost of traditional serial approaches (12). An alternative methodology developed by Hanak (13) that is now referred to as "compositional spread", fabricates continuous multidimensional gradients of different materials, for example by codeposition of two or more components at different concentrations onto a substrate surface. More recently, van Dover and Schneemeyer (14) reported the discovery of new dielectric materials by vacuum sputtering three

Table 1. **Application Areas Open to High Throughput Experimentation**

Application areas	Technical challenges	Impacted products	Economic benefits
• industrial chemicals and monomers	• faster catalyst screening • capability of screening • extremely diverse combinations of catalyst ingredients	• industrial chemicals • engineering thermoplastics • other plastics	• lower cost • lower energy usage • new products based on newly affordable raw materials
• polymers – catalysts – polymer blends – surface modifiers	• faster screening • process optimization	• engineering plastics • thermoplastics	• new products • new markets such as automotive glazing • reduced domestic energy consumption
• ceramics	• thermal barrier coating • optimization • electronic properties • higher strength	• aircraft engines • advanced power machines • conductors • semiconductors • dielectrics • machine tools	• higher engine temperatures • increased service life, and reduction of downtime • higher component densities and speeds • machining of new alloys, increased productivity

different organometallic precursors into a "continuous compositional phase spread" thin film that varies by composition along the x–y plane. New materials with unique chemical, optical, and electronic properties have been discovered, using a variety of parallel screening approaches, for new products (15). Industrial, academic, and Federal laboratories have adopted HTE in polymers (16–20), biomaterials (11), hybrid organic–inorganic materials (22), phosphors (23), and optoelectronic devices such as ZnO-based compound semiconductors for light-emitting diodes (LEDs) (24,25).

One market factor that might correlate with the movement of HTE methods is the current level of spending for R&D in these sectors. Implementation of HTE technologies is expensive; sufficient R&D funds must be available, and acceptable returns on the investment may be precluded in some industries by their profit structure. Aerospace, automotive, biomedical, telecommunications, and computers are the principal end-users of the chemicals and materials sectors. Semiconductor and electronic hardware sectors are materials and device producers (OEMs), and analytical instruments and software sectors provide technology infrastructure. The annual R&D budgets for these firms are an indicator of the leverage that HTE methods can have: assuming a 5% penetration into the infrastructure ($9.7 billion in 1997) and supplier sector R&D ($13.4 billion), ~$1.2 billion in R&D budgets might be assigned to high throughput methods development with a potential downstream increase of $905 billion in sales, excluding pharmaceuticals (26).

2.2. Methodology. The conversion of the traditional discovery process to high throughput experimentation was enabled by the convergence of several technologies: computer software (data warehousing and query engines, molecular modeling, machine control software, and statistics) running on more cost-effective computers; robotics; MEMS (microelectromechanical systems) technologies; and sensors. In effect, research was transformed from the traditional "serial" processes into parallel "factory" processes. Industrial sectors outside of the pharmaceutical industry recognized the attributes of the new drug discovery paradigm and implemented high throughput screening for discovering new materials and developing new processes. Traditional, serial discovery processes rely on the preparation and characterization of individual samples from bench scale (milligrams or grams) to pilot scale (grams to kilograms). The HTE methods can more rapidly sample the same preparation and characterization space *in parallel* using automated laboratory instrumentation at the microgram-to-milligram scale. An emerging trend is to use HTE in process development, as several firms are utilizing multiple microreactors in parallel to scale-up from the discovery phases to manufacturing scales. Eventually, HTE will be applied to product development and customer service when it becomes more automated, simpler, and faster, resulting in a greater probability of commercialization and market penetration. For example, the results from mining the data of an extensive R&D database for polymer blend formulations could be fed into a rapid-screening system that identifies process chemistries in response to customer specifications.

The materials and chemicals industries can leverage, to some extent, the tools developed for drug discovery, ie, from being focused on solution-state synthesis to solid-state materials fabrication. The challenges to the materials scientist arise from the increased degrees of freedom associated with a larger number of parameters that define the design, fabrication, and analysis of a materials library compared to a drug discovery library. The processing of materials typically involves energetic reaction environments, with temperature requirements of hundreds or thousands of degrees Celsius (°C), and pressures of hundreds or thousands of kilopascals (kP). Microscale solid-state samples may also be subject to significant influence from the substrate onto which they are deposited—interfacial effects such as diffusion can produce phenomena that are not reproducible in bulk samples of manufacturing scale. Thus, advanced materials suffer from "scalability", or differences in properties observed in microscale vs. lab-, pilot-, or commercial scale. Finally, solid-state compositions may develop into different (kinetically controlled) metastable structures depending on processing and testing conditions. Most practitioners of HTE validate their sample libraries at every possible process stage ("hit" or "lead") by using control samples, calibrated reference standards, or comparison with bulk samples.

A general process flow for materials discovery is shown in Figure 1.

- Target Definition utilizes expert opinion, hypothesis, market need, and knowledge based on computational chemistry to develop an experimental target. This aspect of research has not changed, however a knowledge of when to use HTE methodologies and its issues might provide a greater scope of experiments to be completed.

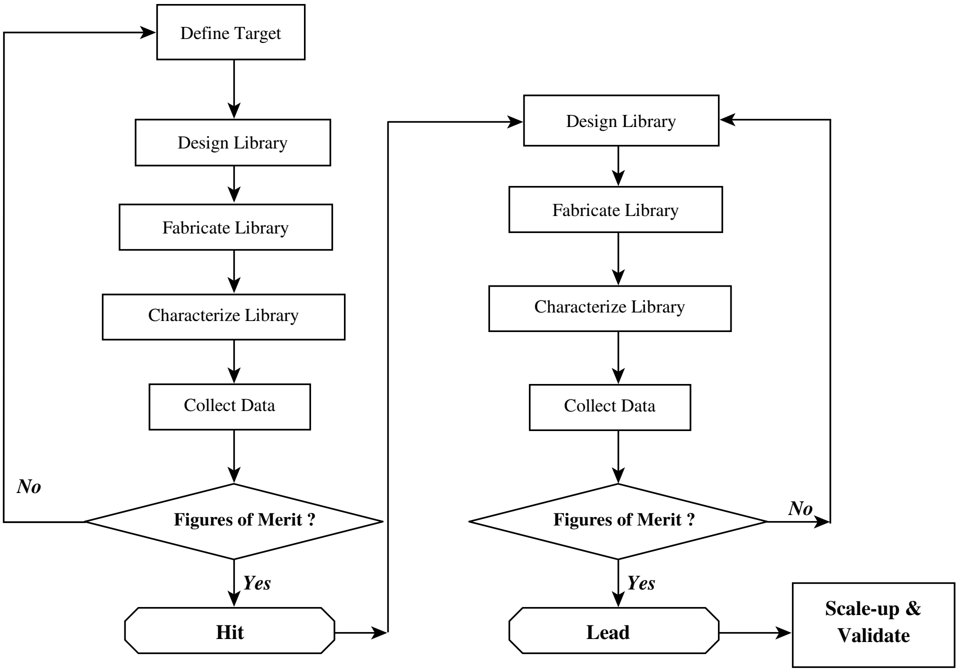

Fig. 1. The key steps of a typical high throughput RD&E process.

- Library Design with computational inputs such as quantitative structure–property relationships (QSPR) and molecular modeling, relies heavily on statistical methods such as Design of Experiments (DOE) (27) or evolutionary approaches (28) to reduce the number of samples in defined sample spaces within the experimental universe or to direct screening to other spaces within the universe. Due to the potentially high number of candidates available in HTE methodology, the design of the sample library requires rational chemical synthesis or process information to reduce the number of samples and experiments without increasing the probability for endless searches, false positives, or false negatives. New tools will have to be developed to enable the integration of this information into molecular- and property-modeling engines. The increased amount of data that can be input into computational engines will require a significant increase in speed, bandwidth and storage. Advanced, high speed quantum calculation programs such as Wavefunction, Inc.'s program SPARTAN (29) and Accelrys' program Cerius (30) will require interfacing with databases and experimental design programs; advances in experimental strategy for dealing with large, diverse chemical spaces, using space-filling experimental designs, predictive algorithms, and optimization techniques.
- Library Fabrication involves the automated deposition and/or processing of an n-dimensional matrix of physical samples. Sample fabrication is highly dependent on specific application areas and will be detailed in later sections.
- Library Characterization in a parallel or massively parallel mode involves the use of robotics and sensors to rapidly and automatically analyze the library of targets for desired properties. It is important to distinguish the characterization of the materials from the measure of their performance. Characterization is highly dependent on specific application areas and will be detailed in later sections.
- Data Collection and Analysis uses data base and artificial intelligence tools—"informatics"—expanded into the more complex realm of materials properties. Informatics can be defined as the computer software that collects and stores raw data and converts that data into information in such a way that it is easily interpreted by researchers; "intelligence" converts information into knowledge, and although there are strong efforts in artificial intelligence, its practice has not yet become widespread (31,32). An informatics engine sits at the front end of the HTE installation as an input into experimental design. It provides hardware control and collects analytical data from instrumentation; it stores and manages large data bases, either external or internal to the organization; and it provides a suitable human-computer interface for visualizing the data to yield knowledge. The underlying software technology must be able to define profitable experimental spaces, permit visualization of complex relationships from large volumes of multidimensional data, and correlate target materials with properties to permit data base queries from a broad spectrum of data mining engines and the development of structure–property relationships. This requires interfacing with data visualization tools at the back end, and

database search and experimental design engines on the front end, while remaining interoperable with enterprise-wide systems for knowledge management and maintaining control of experimental hardware. The technology challenges have been identified by several workshops and roadmapping exercises (26):

- Integrated packages linking modeling, development and management of databases and search engines, hardware control, data visualization, and logistics. Database search engines need to be interoperable with the diverse flavors of databases currently in use;
- Development of Quantitative Structure Property Relationships (QSPR) for materials. This would permit the prediction of advanced materials with known or proposed composition or structure;
- Developing relationships between chemistry, processing, microstructure, metastable states, etc, would enable the design of new materials from atomic level chemistry;
- Development of a query language that links the data with many different query methods;
- Assembly of a high performance data mining toolbox that extends a database management system with additional operators;
- Connection to the diverse metrics in materials design, where important properties are sensitive to broad ranges of length or time scales, eg, from 10^{-9} to 10^{2} m and nanoseconds to years;
- Development of tools to present complex, multidimensional data relationships to the human interface. HTE establishes the new paradigm for the researcher who now must interpret data surfaces and not just data points.

A list of software challanges is given in Table 2. A brief list of companies selling software into this arena is included in Table 3.

Table 2. **Technology Challenges—Software**

Software technology	Challenge
Library design	
statistics	• development of higher order designs
modeling	• (comprehensive review by NSF on computation chemistry is pending)
literature/patent data bases	• query languages; visualization; integration
Informatics	
QSPR (structure–property predictions)	• property prediction, large-scale correlations, integration into experimental design tools
data base query engines	• new languages, genetic programs • inter-operability, enterprise-wide integration

Table 3. **Software Companies**[a]

Company	Web site
Accelrys (in June, 2001 combined Oxford Molecular, Molecular Simulations Inc., Synomics Ltd., Genetics Computer Group, Synopsys Scientific Systems)	*http://www.accelrys.com*
Advanced Chemistry Development	*http://www.acdlabs.com*
CambridgeSoft	*http://www.camsoft.com*
Cambridge Crystallographic Data Centre	*http://www.camsoft.com*
Chemical Abstracts Service	*http://www.cas.org*
Daylight Chemical Information Systems	*http://www.daylight.com*
SciVision	*http://www.scivision.com*
Spotfire	*http://www.spotfire.com*
Tripos	*http://www.tripos.com*

[a] Ref. 24.

2.3. Commercial Environment. Materials manufacturers are utilizing several business scenarios to obtain HTE capabilities: (*1*) by developing internal capabilities; (*2*) by contracting with service providers having a core competency in high throughput discovery methods; (*3*) by developing an independent consortium or alliance partnership with individual tools providers; and (*4*) by various combinations of these scenarios. These events signal a clear trend that the materials industry is beginning to outsource (subcontract) their front-end discovery efforts to smaller external entities. A number of chemical and materials-producing companies have implemented HTE by internal growth (Table 4), most commonly realizing adequate return on assets by placing it in a corporate or central R&D facility to benefit more than one business unit. There are currently seven companies known to be either performing front-end R&D on a contract basis, or developing integrated systems for large materials manufacturers utilizing HTE R&D (Table 5).

There have been a variety of models for entering the area of combinatorial catalysis through strategic partnerships. Two notable consortia have developed:

1. Combicat, the European Consortium on Combinatorial Catalysis, was formed in August 2001 in Budapest, Hungary (23). Current industrial members include Eni Technologie, DSM Research B.V., Engelhard de Meern, AMTEC GmbH, and Millennium Pharmaceuticals Ltd. Academic partners include the Institut Francais du Petrole, the Dutch Energy Research Foundation and Environment Department of Fuels Conversion, Institut de Recherches sur la Catalyse (Villeurbanne), the Berlin Institute for Applied Chemistry, and the Universidad Politecnica de Valencia. The objectives of the consortium are to develop both tools and methodologies, with the goal of achieving a yearly throughput of >100,000 samples (discovery phase) leading to 1–5 catalysts entering commercial development. The effort will encompass sample fabrication through data handling and informatics issues. Catalyst discovery will focus on relatively generic processes: the oxidative dehydrogenation of ethane, water–gas shift reaction, the

Table 4. **Companies Implementing Internal HTE Efforts**

Company	Application area	Partner/supplier
3M	polymers	self
Akzo-Nobel	catalysts	Avantium Technologies
Albemarle	catalysts cocatalysts polymer additives	self
Avery Dennison	polymer coatings	self
BASF	catalysts advanced materials polymers	hte GmbH Symyx Technologies
Bayer AG	advanced materials	Symyx Technologies
BP-Amoco	catalysts	self
Celanese	catalysts	Symyx Technologies
Ciba Specialties	pigments polymer additives	Symyx Technologies
Dow Chemical	polyolefin catalysts specialty chemical catalysts	Symyx Technologies
DSM	catalysts	Cambridge Combinatorial
E. I. DuPont de Nemours	catalysts	self
Eastman Chemical Company	catalysts	self
Energiser	battery materials	Symyx Technologies
ExxonMobil	polyolefin catalysts	Symyx Technologies
General Electric CR&D	catalysts, polymers	self
ICI	catalysts	Symyx Technologies
Lonza	specialty materials	Symyx Technologies
Rohm & Haas	polymers	self
TexacoChevron	catalysts	hte GmbH
Unilever	personal care polymers	Symyx Technologies
UOP LLC	catalysts	self, with SINTEF
W. R. Grace	catalysts	Avantium Technologies

isomerization of ethylbenzene into *p*-xylene, the alkylation of toluene with methanol into styrene, and the selective hydrogenation of crotonaldehyde.

2. The Measurements and Standards Laboratories (MSL) of the National Institute of Standards and Technology (NIST) (Gaithersburg, Md.) have initiated an industry consortium in the area of polymer science (34). The NIST MSL are uniquely qualified to participate in this area: NISTs broad capabilities for scientific research and technology development address major challenges of high throughput methods implementation.
3. The NIST Advanced Technology Program (ATP) is supporting research within the NIST MSL in the areas of polymer array scaffolds for tissue engineering, two-dimensional infrared (ir) array detection of inorganic and organic substrates, X-ray and microwave measurement of dielectric ceramic thin films, analysis of dopants in compound semiconductor thin films, X-ray studies of supported catalysts, and genetic programming of data query engines. The largest contribution ATP has made in this field is through cost-shared funding to the private sector for a variety of research projects in catalysis, polymer coatings, and electronic materials.

Table 5. **High Throughput Methods Providers for Advanced Materials**

Company	Parent	Financing/partnerships, major clients
Symyx Technologies	(A. Zafaroni, etc)	IPO-11/20/99
	(Santa Clara)	Hoechst AG, Celanese, Bayer AG, BASF, B.F. Goodrich, Dow Chemical Co., Unilever, Argonaut (equipment manufacture and distribution), Agfa, Applied Biosystems, Merck, Prolinx, ExxonMobil, Instituto Mexicano del Petroleo (IMP)
hte GmbH (Heidelberg) hte North America (San Diego)	MPI-Kohlenforschung, BASF	MPI-Kohlenforschung, BASF (client), private financing, MSI/Pharmacopoeia
Physical Sciences Division, SRI International (Menlo Park)	SRI International	Internal, clients
Thales Technologies (Zurich)	ETH-Swiss Federal Institute of Technology (Zurich)	N/A[a]
CombiPhos Catalysts, Inc. (Princeton)	Dupont de Nemours (Wilmington)	N/A[a]
NovoDynamics (Ann Arbor, MI)	-Catalytica Advanced Technologies/NovoTech -Nonlinear Dynamics	N/A[a](Announced June 2001)
Torial LLC	UOP LLC/SINTEF	N/A
Avantium NV (Amsterdam) Avantium Inc. (Columbia, MD)	Shell Chemical Co. (Amsterdam)	Universities of Delft, Twente, Eindhoven; the government of The Netherlands; GSE, Inc.; W.R. Grace, others

[a] Not available = N/A.

3. High Throughput Experimentation for Industrial Catalysis

3.1. Economic Benefits of HTE Methods in the Chemicals Industry.

The U.S. chemical process industry has annual revenues of over $400 billion, and its products enter many industry sectors, with economic impact of >$1.2 trillion in downstream product sales and service. Catalysts play a key role in the manufacture of well >$3 trillion in goods and services of global gross domestic product annually. Royalties and fees from technology process licensing in chemicals, polymers, and refining exceed $3.5 billion annually and catalysts sold in the merchant market exceeded $9 billion last year (35). Production of chemicals from industrial catalysts provide significant value to the United States in comparison to the global economy, as shown in Tables 6 and 7. Catalyst market is listed in Table 8.

Table 6. **Catalysts for Chemicals Production (1997 Demand, 000s mt)**

Process	North America	Rest of world
aromatics:	37	123
organic synthesis	276	174
oxidation	64	324
$NH_3/H_2/CH_4$	135	555
hydrogenation	88	230
dehydrogenation	6	135
Total	*606*	*1,541*

Table 7. **Chemicals Produced by Catalysts (1997 Demand, 000s mt)**

Product	North America	Rest of world
aromatics	13,563	31,404
organic synthesis	4,226	7,326
oxidation	85,721	200,381
steam reforming	27,420	135,570
hydrogenation	39,044	96,760
dehydrogenation	5,852	14,492
Total	*175,826*	*485,933*

Global market pressures force the chemicals industry to continuously improve the productivity of their manufacturing processes and their research and development (R&D) facilities. In the last two decades, the market drivers—shorter innovation cycle times, higher product quality at lower cost, with reduced environmental impact from manufacturing—have constrained industrial R&D to near-term, applied research and process development at the expense of discovery and invention (36), resulting in a relatively flat R&D funding trend.

The penetration of HTE methods in industry can be measured by the amount of research money expended on this technology. Modest growth might also be expected because of the lower revenues from materials-based industries, where profits and revenues are significantly lower, and development times are shorter, compared to the pharmaceutical industry (37,38).

Table 8. **Catalyst Market, North America ($ millions)**[a]

Market	1995–1996	1998	2001
refining	791	813	909
chemicals	681	720	766
polymerization	380	436	520
emissions control	1070	1201	1390
Total	*2922*	*3170*	*3585*

[a] See Ref. 4.

Another measure of the growth of HTE methods is the commercial impact of the materials discovered using this technology. For the end-user, there will be nothing to distinguish a material discovered using HTE from a material discovered using “traditional” technology. Certainly, over time, it is likely that materials discovery using HTE itself will become the “traditional” research methodology (39).

With rising economic demands for higher efficiency and productivity in research and development, HTE methods are increasingly being implemented to bring more catalysts per unit time to the marketplace. High throughput automated synthesis and advanced screening technologies are now being applied to the discovery of more efficient homogeneous as well as heterogeneous catalysts and materials. The HTE process allows the exploration of large and diverse compositional and parameter spaces by establishing an integrated workflow of rapid parallel or combinatorial synthesis of large numbers of catalytic materials, subsequent high throughput assaying of these compounds and large-scale data analysis. The number of experiments that can be screened has risen by orders of magnitude, and has resulted in a much higher probability of discovering new catalysts or materials.

Demands for more effective catalysts in the polymer, specialty chemical, and environmental markets are driving growth by 5%/year, and catalyst suppliers are reacting to lowered sales in the commodity markets through consolidations and strategic alliances with process developers, suppliers, and customers. High throughput experimentation is speeding up the discovery process with the expectation that new catalysts and corresponding intellectual property will be produced faster and more efficiently (40). This has been facilitated since many of the HTE methodologies and tools for the CPI have leveraged the developments made in HTS and combinatorial chemistry in the pharmaceutical industry.

In an effort to define what potential value HTE methods could bring to a chemical company, Busch (41) surveyed 30 experts from the plastics industry to define the effort, costs, and potential profits in discovering a mid-level “engineering polymer” such as polycarbonate, with global annual consumption of around 500 million kilograms and a market opportunity of $2 billion. Busch observed that, using traditional laboratory methods, the first year for revenue generation is 12 years following the discovery phase, and financial break-even occurred on average 17 years after ideation; a net present value (NPV) of $10 million was assumed at project start. The HTE methods, on the other hand, reduced the time interval for both the discovery phase and scale-up by 1 year each, and this earlier market entry granted the plastic a 15% price premium; even with $6 million in depreciated capital outlays for equipment, the present value was calculated to be $37 million. Busch concluded that, at least for a high valued polymer, HTE methods are financially viable to implement based on return on investment.

Similar studies have been completed using discounted cash flow (DCF) in a pro forma estimate of NPV for traditional vs. HTE methods applied to the discovery phase of a pharmaceutical intermediate. Using a published case study (42) as a basis for time and personnel reductions, and a generic pro forma spreadsheet (43), the difference between a 10- and a 6-year commercialization period resulted in increased NPV from ∼$200 to >$250 million. This difference was attributable solely to the decreased time in the discovery phase; the general feeling of this industrial community is that additional value would be generated using HTE methods to reduce the time spent in the process development and precommercialization stages.

Neither of these studies take into account intangible productivity gains (44) introduced by HTE methods. For example, the ability to scan literally 100–1000 times more samples allows a trained research team to explore more and different areas of chemistry that would not otherwise be possible under typical industrial time constraints. As indicated earlier, Symyx reported examples of ternary catalysts with substantially improved performance over binary catalyst mixtures as reported in the open literature and patents. Pioneering researchers are showing that HTE increases serendipity, as it is a powerful method to generate and evaluate a large number of catalysts in very short time (45). Recently, both UOP LLC (46) and DuPont (47) announced the commercial utilization of new catalysts developed with HTE methods in significantly less time than using classical methods. UOP confirmed that their commercialization cycle time has been reduced from a period of eight to ten years using traditional methods to a period of three-to-five years using HTE.

The entry costs for obtaining HTE capabilities can be very high—in the neighborhood of $10–20 million for very high throughput systems. Many companies, such as UOP and DuPont, have centralized HTE facilities that were developed internally to service their business units. Alternatively, firms of all sizes are exploiting alliances with external contract research firms, such as Symyx Technologies, hte (Heidelberg, San Diego), Thales Technologies (Zurich), CombiPhos Catalysts (Princeton) and Avantium Technologies (Amsterdam), as a route to obtaining competitive advantages. The subcontactors exercise business models based on sharing intellectual property and/or equity with partners to develop methodologies, technology, and applications, or are obtaining royalties from licensing agreements.

As noted in the previous section, Combicat, the European Consortium on Combinatorial Catalysis, was formed in August 2001 in Budapest, Hungary (48). Eleven European partners from seven countries shall assess the potential of combinatorial chemistry (HTE) applied to five generic heterogeneous catalyst systems (the selective hydrogenation of crotonaldehyde; water–gas shift reaction; dealkylation–isomerization; alkylation of toluene with methanol; and oxidative dehydrogenation of ethane) and facilitate the development of precompetitive tools and methodologies across the members. Members include academic and industrial research institutions, experienced small- and medium-sized enterprises (SMEs), catalyst manufacturers, end users, and engineering companies.

The period 2000–2002 has shown significant advances in the development of HTE approaches to the discovery and optimization of catalysts. The highlights include the development of modular approaches to the synthesis of libraries of organometallic complexes and catalysts, novel indirect screening methods, and automated syntheses and screening of high density solid-state libraries (49).

This article provides an overview of selected advances in this rapidly growing field over the past several years, advances that have taken place in academia and industry. Review articles provide more detail in different areas of HTE applied to catalyst discovery (50–62) and a web site (http://www.highthroughputexperimentation.com/links/CatMat.htm) is focused on different application areas of catalysis.

3.2. Application Areas. *Chemical Processing and Refining Catalysts.* Preliminary work in HTE methods applied to homogeneous organometallic catalysis began in 1998, utilizing instrumentation from the pharmaceutical sector. The pharmaceutical tools had previously been applied almost exclusively to aqueous solution-based systems, and modification was needed by early adopters to synthesize libraries under anaerobic conditions using organic solvents (64–67). Instrument manufacturers currently offer robotic sample handling to accommodate anaerobic conditions and higher pressures and temperatures (68), which has opened the methodology up to additional commercial research facilities to both rapidly synthesize organic ligands and organometallic complexes and to screen them for catalytic activity in chemical reactions.

Supported homogeneous catalysts were also studied using traditional methods analogous to pharmaceutical combinatorial chemistry, eg, novel phosphine and phosphine oxide ligands were prepared on polymeric supports for metal-complexed catalysts (69–71). Albemarle (Baton Rouge, La.) has developed new catalysts for the Suzuki coupling reaction of aryl bromides using palladium–phosphine and palladium–ligand complexes (ligand = heterocyclic carbenes and diazabutadiene) (72). Crabtree, Janda, Finney, and others reported the combinatorial synthesis of biomimetic catalysts using metal complexes attached to supports using linking ligands, where binding to an active site is controlled via substituents, that is by molecular recognition (73).

Heterogeneous catalysts account for ~80% of the global catalyst market. As shown in Figures 2–4, there is a substantial market for industrial catalysts in the areas of refining, chemical intermediates, polymer manufacture, and emissions control catalysts for environmental applications. The primary chemical processes are production of aromatics, oxidation catalysis, hydrogenation, miscellaneous organic chemical intermediates, ammonia production, and dehydrogenation of olefins. And would have been the leading application for HTE were it not for the significant technical barriers (see below) that slowed the use of HTE methods for these applications. Symyx Technologies (74), hte GmbH (75) and

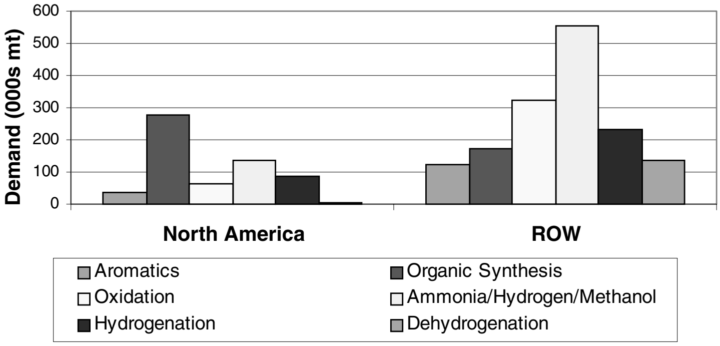

Fig. 2. Catalyst demand for chemicals production (1997), North America vs. rest of world (Row).

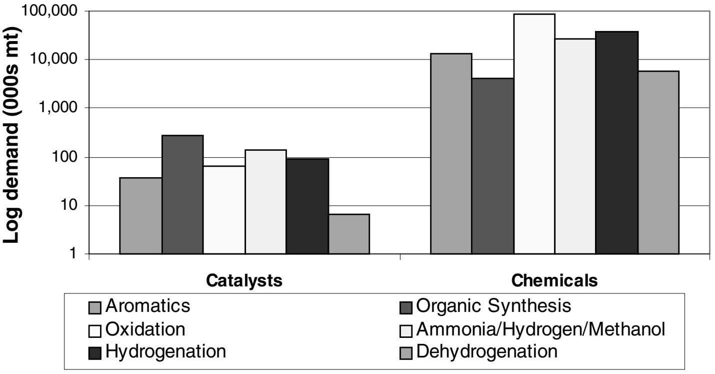

Fig. 3. Catalyst demand vs. chemical production, North America (1997).

others (76,77) reported findings for a variety of reactions using supported catalysts for chemicals processing. Symyx has entered into a discovery and licensing agreement to develop novel catalysts for the manufacture of chemical intermediates with Lonza, where Symyx has validated chemistry platforms to discover a broad range of catalysts, including chiral chemistry, hydrogenation, aromatic cross-coupling, Friedel Crafts catalysis and selective oxidation.

Refining Catalysts. The United States demand for petroleum refining catalysts was ∼$1,075 million in 2000, and is expected to rise 3.5% annually to $1290 million by 2005 (2,561 million kg rising to a volume of 3067 million kg) (78). Market activity is summarized in Table 9.

Increased demand is mainly attributed to the increasing need for environment-friendly refinery and chemical products (79), especially for reformulated and other less polluting gasolines—a result of proposed gasoline sulfur limits, declining crude quality, and a move to new, higher value products. Broader trends in the crude oil industry also play a role, especially pricing, industry consolidation, and the quality of crude stocks.

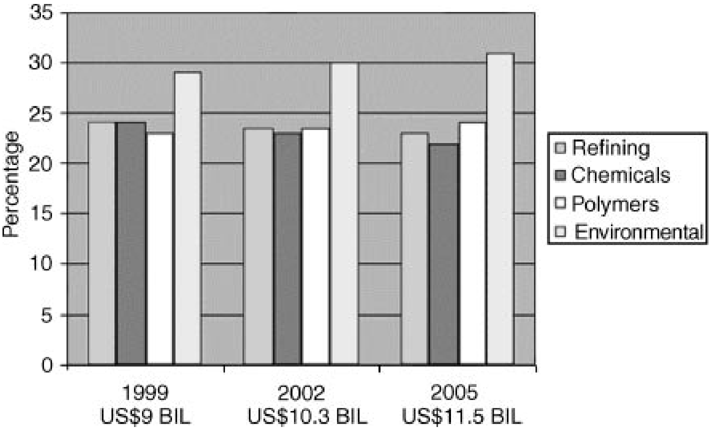

Fig. 4. Catalyst demand vs. chemical production, North America (1997).

Table 9. **Catalytic Refining and Chemicals Production (million lb), North America (1997)**[a]

Application	2000	2005 (est.)
catalytic cracking	520	545
alkylation	5030	5490
hydrotreating	50	55
hydrocracking	10	15
reforming	5	5
others	20	25

[a] See Ref. 45.

High throughput synthesis of catalytic zeolites has been reported by Bein and others (80). The research effort in high throughput synthesis and screening of heterogeneous catalysts at UOP and the Norwegian research institute SINTEF has focused on the hydrothermal synthesis of microporous materials and subsequent deposition of supported noble metal catalysts for fluid bed reactors. An automated reactor developed by SINTEF allows 48 zeolite syntheses to be carried out simultaneously (81). The supports are analyzed using X-ray diffraction (XRD) and scanning electron microscope (SEM) in a high throughput process. The analysis gives them information about zeolite structure as well as particle size and shape. Catalysts are tested for performance in reactors that simulate production-scale equipment. For example, UOP developed a small array of fluid bed reactors that were used to discover and scale up catalysts that will be commercialized in 2002 (48). UOP/SINTEF have utilized HTE to screen >2500 catalysts in 6 months, compared to previous, traditional catalyst discovery programs at UOP that could screen 271 catalysts in 3 years (83).

Fuel Cell Catalysts. A significant growth area for catalysts includes fuel cells for stationary and vehicular electrical power. In a fuel cell, hydrogen fuel is fed into the anode, oxygen from air is fed into the cathode, and the reaction is completed via an internal proton-conducting membrane and external electron-carrying circuit to generate water, heat, and electricity.

Because there is already an extensive infrastructure for natural gas for stationary source applications, and gasoline, alcohol, propane, liquefied natural gas (LNG) and diesel fuel for mobile applications, conversion of hydrocarbons to hydrogen is preferred over building a new infrastructure to support hydrogen distribution. Catalysts are therefore a crucial part of fuel cell systems because they convert hydrocarbons into hydrogen inside a secondary unit called a reformer, enabling the fuel cell to generate electrochemical energy from hydrocarbons. The reformer could be attached directly to a fuel cell or could be in a centralized location for distribution to multiple fuel cells. Relatively clean hydrogen is required for fuel cells, and its production from hydrocarbons is well known, yet there remain significant technical challenges, namely being able to provide enough heat; removal of sulfur from the hydrocarbons before it reaches the reformer; use of more robust catalysts; and removal of carbon monoxide impurities.

The catalyst industry has been pursuing fuel cell reformer catalyst technology, however, the open literature for using HTE methodologies in this area is not extensive. Johnson Matthey has been conducting research in fuel cell catalysts using HTE for some time, and has an agreement with energy company TXU Europe (Wherstead, U.K.) and fuel cell developer Energy Systems (West Palm Beach, Fla.) to construct and evaluate a fuel cell system for residential applications (84). Fagan, of DuPont Experimental Station, reported the rapid automated screening of modified electrode surfaces for electrochemical activity (85). Mallouk, at the Pennsylvania State University, reported (86) using arrays of electrodes that contained hundreds of unique combinations of five elements (Pt, Ru, Os, Ir, and Rh) screened for activity as oxygen reduction and hydrogen oxidation catalysts; he found that the ternary catalyst $Rh_{4.5}Ru_4Ir_{0.5}$ is significantly more active than the previously described Pt_1Ir_1 bifunctional catalyst. Symyx Technologies has reported (87) some activity in this area, and a general review article of this field was written by Service (88). Among the objects of the invention are the preparation of catalysts based on platinum, ruthenium, and palladium, which have a high resistance to poisoning by carbon monoxide thereby improving the efficiency of a fuel cell, decreasing the size of a fuel cell and reducing the cost of operating a fuel cell. The inventions (89) are directed to ternary and quaternary metal alloy compositions, eg, PtRuPd and PtRuPdOs.

Polymerization Catalysts. Higher performing plastics are making polymerization catalysis the fastest growing segment in the catalyst industry. Freedonia reported that demand for metallocene and other next-generation polymerization catalysts is growing fast, although conventional catalysts, including Ziegler-Natta catalysts, and initiators, accounted for >90% of U.S. polymerization catalyst demand in 1998 (89). Metallocene (single-site) catalysts are expected to displace Ziegler-Natta catalysts by the end of the year 2010, with prices lowered from the increased economies of scale. Metallocene catalyst demand is being driven principally by demand for polyethylene that has improved performance characteristics that can be obtained from these new catalysts. A 9%/year increase in demand for polyolefins in the United States, to >$1 billion/year in 2003, is estimated, with global demand reaching 5.9 million tons in 2010.

Polymerization catalysts received early attention from researchers utilizing HTE methods for both discovery and for process development in the area of olefin polymerization. Symyx Technologies developed alliances with leading chemical and polymer manufacturers such as BASF, Bayer, Celanese, Lonza, Sumitomo, and Unilever, to develop new catalysts and processes (90). Symyx is working with Dow Chemical in the area of non-metallocene single-site catalysts for ethylene–styrene copolymers and polypropylene (91); with ExxonMobil to develop petrochemical catalysts; and with ICI for the discovery of specialty polymers and other materials for high performance coatings, binding agents for textiles, and specialty adhesives (92).

Extensive studies have been conducted independently by Symyx (93). A solid-phase protocol has been developed that allows for the parallel synthesis, screening, and chemical encoding of nickel(II) and palladium(II) olefin-polymerization catalysts. These catalysts display activity profiles comparable to the analogous homogeneous catalyst systems prepared by traditional methods. A chemical encoding strategy has also been developed that enables the chemical history of pooled solid-phase catalysts to be evaluated.

Table 10. **Environmental Catalysts**

Market ($ million)	1999	2005 (est.)
motor vehicle	$1588.0	$1965.0
stationary	$855.0	$1063.0
other	$170.0	$526.0

Albemarle intends to develop new families of activators for metallocenes and other single-site catalysts using HTE (60). Although there have been many years of research in this area, the precise structure of methylaluminoxane (MAO), used as an activator for metallocene single site catalysts, is unknown and the manner in which it interacts with metallocenes is poorly understood. It is widely believed that actual utilization of the MAO under catalytic conditions is under 10%, and large excesses are usually used in processes to ensure activity. Albemarles' goals are to make the activators highly efficient, stable, lower-cost, and a "drop-in" replacement into existing production processes.

Environmental Catalysts. Environmental catalysts are multifunctional, supported catalysts containing noble metals that reduce nitrogen oxides (NOx) and oxidize carbon monoxide and unburned hydrocarbons in mobile sources (automobiles and trucks). In stationary sources (power plants and refineries), environmental catalysts reduce sulfur oxides (SOx). The worldwide emission-control catalyst market was $2.6 billion in 1999, and it should grow 4%/year, to reach $3.6 billion by 2005 (95). Table 10 summarizes the markets for environmental catalysts.

Within the United States, demand for emission control catalysts is being driven by U.S. Environmental Protection Agency (EPA) regulations limiting emissions of pollutants from stationary sources that will go into effect in May 2003. Forty-eight catalytic hydrodesulfurization plants in 34 states will have to be expanded or upgraded, with costs estimated to be $3.5 billion (95).

New EPA regulations aimed at reducing sulfur content of gasoline and diesel fuel for automotive and truck applications drives a substantial R&D effort in the United States for new refinery catalysts as well as sulfur-tolerant automotive and truck catalysts (64,95). The regulations have translated into a global effort to develop lowered sulfur content in fuels since the new emissions catalysts are easily poisoned by sulfur. The international effort is also focused on catalysts with reduced sulfur sensitivity that will significantly reduce NO_x emissions from gasoline and diesel engines. Lean burn (high oxygen/fuel ratio) catalysts for gasoline-powered vehicles is something of a Holy Grail for catalyst researchers, and this area has yet to see a commercial product despite intensive efforts over many years. For this reason, research using HTE methodologies applied to lean burn catalysts has obtained more attention than other areas of environmental catalysis.

The German firm Degussa Metals Catalysts Cerdec (dmc^2), a major automotive catalyst producer, is spending ~5% of its $4.1 billion in sales on traditional and HTE catalyst research and development (96). Another firm with German roots, hte GmbH (Heidelberg and San Diego), is investigating the catalytic reduction of NOx under lean burn conditions, where current catalysts lack sufficient durability, activity and/or selectivity for commercial automotive applications (62). In October, 2001, the U.S. DOE awarded Engelhard (New Jersey) a total of \$4.5 million in funds for the development of fuel processors for transportation applications and the use of combinatorial catalysis for the reduction of nitrogen oxide emissions in collaboration with General Motors, ExxonMobil, and Los Alamos National Laboratory (97).

Senkan and co-workers at UCLA reported (98) the selective catalytic reduction of nitrogen oxide (NO) by propane by screening a library of 56 quaternary Pt-Pd-In-Na catalyst mixtures prepared by robotically impregnating γ-Al_2O_3 pellets with various solutions. The group evaluated a microreactor array using mass spectrometry, however, the performance of the entire library under lean burn conditions was poor.

Symyx reported the testing of a 56-member catalyst library consisting of silver-, cobalt-, copper-, and indium-impregnated alumina support in the reduction of NO_x by propane under lean conditions in the temperature range 400–500°C. The catalyst data was acquired by a system of 64 microreactors in parallel (99). In another study of de-NO_x catalysts (100), Symyx applied an HTE approach to the design and screening of the exchange cations in ion-exchanged ZSM-5 by investigating the adsorption energies of NO and water. There are no reports that the catalysts will be commercialized.

3.3. Methodologies. The application of high throughput discovery and process development for chemicals and materials will drive the enabling integration of a hardware- and software-based infrastructure toward specific product applications. The long-term vision shared by many researchers is to have high throughput research become part of expanded enterprise-wide systems that include tools for hardware interfaces, technology assessment/decision, and logistics (Fig. 5). Because HTE is currently highly capital intensive, with start-up

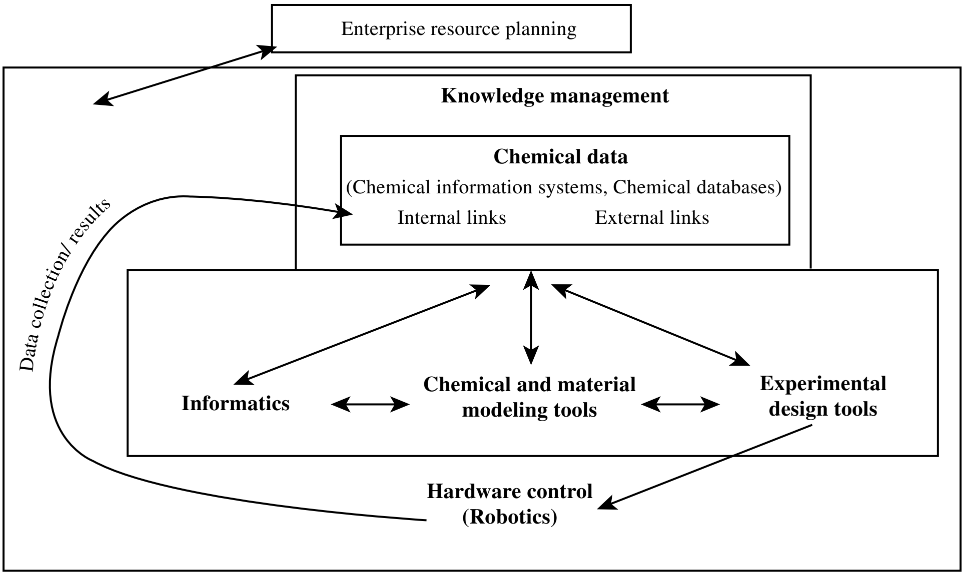

Fig. 5. The integration of software systems.

costs in the range of \$8–20 million, discontinuous innovation in generic and/or modular hardware and software technologies will be necessary to drive down costs and facilitate its implementation in the industrial sectors that have lower returns on R&D investment, such as exist in CPI and materials sectors.

The methodologies inherent in high throughput experimentation for catalysts can be categorized according to design of the experimental space (Library Design), data capture and information retrieval (Informatics), library synthesis or fabrication, and library characterization.

Library Design. The number of possible combinations of parameters relevant for catalysts is too large to try them all, even using very high throughput methods. A methodology for defining boundary sets for reaction conditions and constituents is therefore necessary before libraries are fabricated. The design phase is based on the expert knowledge of the researchers along with outside information, eg, patent and literature databases, previous experimentation, or molecular modeling. Rational chemical synthesis or process information needs to be input to reduce the number of samples and experiments without increasing the probability for endless searches, false positives, or false negatives. Technological challenges include new tools that enable the integration of this expert knowledge and knowledge assets into molecular- and property-modeling engines. The increased amount of data that can be input into computational engines will require a significant increase in speed, bandwidth and storage.

Currently, there are advanced, high speed quantum calculation programs (101) such as Wavefunction, Inc.'s program SPARTAN and Accelrys' Cerius that attempt to interface with databases and experimental design programs. For example, Accelrys' simulation software provides unique tools for studying diffusion and adsorption in microporous materials. In the Insight II product line, scientists can construct models of zeolite structure using the structure determination tools. An ensemble of trial guest molecules can be generated and used to probe the zeolite lattice. A detailed picture of the factors affecting diffusion and sorption can thus be built up—assisting zeolite selection and design prior to synthesis and testing, and helping to understand the results of such tests. Cerius2 predicts adsorption sites and binding energies of molecules through the C2 · Sorption module. Diffusion and the dynamic behavior of the framework can be studied using the C2 · Minimizer and C2 · Dynamics modules, together with the zeolite force fields in the C2 · Open Force Field.

The goal of materials researchers is to develop experimental strategies for dealing with large, diverse chemical spaces, using designs that explore all of the experimental space, predictive algorithms, and optimization techniques. Baerns utilized an evolutionary method for selection and optimization of heterogeneous catalytic materials that was developed and validated for the oxidative dehydrogenation of propane using various oxides (V_2O_5, MoO_3, MnO_2, Fe_2O_3, GaO, MgO, B_2O_3, La_2O_3) as primary components for the generation of catalytic materials (102). Briefly, the method relies on random selection of generations of catalysts using Monte Carlo techniques. Future generations of catalysts are created through random mutation of previous generations to give variations in the catalyst composition. In practice, one needs between 30 and 100 generations to find the best catalyst (103).

Fagan demonstrated an analogy for homogeneous catalysis based on the models of diversity used in drug discovery. A 96-member "pyridine" library consisting of both rationally chosen and "random" members was used to screen Ullmann ether forming reactions (104). He constructed a large library of ligands to screen for lead homogenous catalysts, then screened highly diverse compounds in an experimental space based on performance closest to a lead catalyst. He found that using a diversity model produced a larger fraction of ligands of increased performance than did the "rational" methods used traditionally by catalyst chemists.

"Hill Climbing" is a classic method for developing diversity where the direction of change of catalyst composition, eg, is calculated by finding the optimum in a multidimensional plot. This can be the fastest road to success, but one needs a good starting point, otherwise, there is a risk of obtaining a local maximum and never finding the best catalyst (105).

Informatics. Informatics software contains integrated packages linking modeling, development and management of data bases and search engines, hardware control, data visualization, and logistics. Data base search engines need to be interoperable with the diverse flavors of databases currently in use.

Other challenges have been noted in the community (106–108):

- Development of QSPR for materials will permit predictions of compositions based on needed properties.
- Acceleration of the design process from atomic level chemistry to engineering design by developing relationships between chemistry, processing, microstructure, etc, and processing involving metastable states, etc.
- Development of a query language for linking many different methods for querying the data with appropriate query optimization methods.
- Assembly of a high performance data mining toolbox that extends a database management system with additional operators.
- Connection to the diverse metrics in materials design, where important properties are sensitive to numerous ranges of length or time scales.
- Development of tools to present complex, multi-dimensional data relationships to the human interface. HTE establishes the new paradigm for the researcher who now must interpret data surfaces and not just data points.

Symyx's Renaissance Software Components includes Library Studio (chemical equations, mapping, recipe file databasing and export); Impressionist (hardware automation); Epoch (high throughput instrument control, data acquisition, viewing, workflow and data management software); Oracle database; and PolyView (searching and viewing data). Symyx has obtained a European patent that claims on computer- implemented methods, programs and apparatus for designing a combinatorial library of materials (109).

Synthesis and Library Fabrication. In the pharmaceutical industry, new drug candidate molecules undergo chemical analyses such as gas chromatography, nuclear magnetic resonance (nmr) spectrometry, mass spectroscopy, fluorescence spectroscopy, while "performance" is measured by the response of a biological receptor (*in vivo* or *in silico*). Catalysts, on the other hand, require performance-based characterizations to correlate to manufacturing realities, in addition to analyses for catalyst structure and composition. Analysis for catalyst performance (selectivity and conversion) requires measurement of products produced by the catalyst, correlated (indexed) back to known or presumed catalyst composition and structure. This may be especially difficult in heterogeneous or supported catalysts for at least two reasons:

1. Since microscale solid-state samples are influenced by the substrate onto which they are deposited, interfacial effects such as metal diffusion into a substrate or activity at certain crystalline defects may not be reproducible with bulk catalyst samples obtained from large-scale production. Thus, catalyst development using microscale screening can suffer from "scalability" issues, nonlinear correlations between microscale results and observed lab- or pilot-scale (bulk) properties at fundamental levels.
2. Solid-state compositions may develop into different (kinetically controlled) metastable structures depending on processing and testing conditions. Therefore, sample libraries must undergo validation at every process step.

Automated hardware for processing catalysts differs from small molecule drug discovery tools. Materials processing typically involves more energetic reaction environments than pharmaceutical processing. The leverage of tools developed for drug discovery, eg, activity-focused/solution-state systems, to solid-state materials, is challenging due to the diversity of potential design, fabrication, and analysis parameters. The ability to utilize data obtained from libraries of microscale samples will require better scientific understanding in the areas of interfacial solid-state interactions and composition–structure–property relationships. The transfer of traditional *serial* research methodologies to multidimensional *parallel* methodologies will require the integration of previously diverse computational and characterization tools for sample library design, sample library fabrication, characterization, and informatics. Other technical needs have been identified by industry (Table 11) (106,110).

Hardware technologies for HTE catalyst library fabrication and analysis are emerging from primary applications in other arenas. Micromachines and microreactor technologies (MRT), based on microelectromechanical systems (MEMS), will address the need for higher library densities, facilitating reduced raw materials costs for library fabrication, and economies of scale and modularity in laboratory instrumentation. The Institut für Mikrotechnik Mainz in Germany (111) and the Zentrum für Werkstoffe in der Mikrotechnik, Karlsruhe (112) are two of several European groups working on microreactor technologies. Research in the United States is centered primarily at the Pacific Northwest National Laboratory (113), the Massachusetts Institute of Technology, Microsystems Technology Laboratory and at Oak Ridge National Labs. Collaboration between DuPont Experimental Station and Massachusetts Institute of Technology has produced a circuit board-level discovery plant containing modular, socket-borne catalytic reactors with integrated fluidics control, heat transfer, separation, and mixing for high throughput discovery and process development (114).

Table 11. **Technical Challenges for Catalyst Testing**

Technology	Challenge
library screening	
thermal properties	• thermal conductivity
optical characterization	• fluorescence, luminescent properties
mechanical properties	• ablation
chemical properties	• molecular weight distribution
	• polymer architecture/morphology
	• turn-over, selectivity, conversion
library processing	
control of physical environment	• control of temperature and pressure over library array with control over individual sample sites or wells
control of chemical properties	• sample size-control of diffusion, mass transport properties, etc
	• interactions with catalyst support or solvent
library fabrication	
micro/ink jet	• reproducible drop size, consistent composition
robotic pipeting of nanoaliquots	
vacuum deposition	• reduction of cross-talk between samples, across substrate surface
thin-films sputtering, etc	
microreactor technologies (MRT)	
systems integration	• development of standards for modular component interconnections
	• on-chip sensors and electronics
reactor design	• process control devices tuned to MRT
	• modeling for fluid flow, heat and mass transfer
manufacturing processes	• substrates: glass, polymer, metal
surface micromachining using wet or dry chemical etching, laser ablation, mechanical micromilling, LIGA processes	

Fabrication of solid-state materials libraries may require deposition of metal oxides onto substrates, using, eg, microjet, laser ablation, or vacuum deposition (PVD, CVD) of oxide precursor followed by annealing, oxidation, reduction, etc. Heterogeneous and homogeneous catalysts are also made with robotic solution transfer using equipment modified from drug discovery applications. While fully automated library fabrication is desired, many laboratories manually prepare libraries under inert atmosphere conditions using standard weighing and solution transfer techniques if their throughput does not justify the expense of robotics.

In an effort to address the specific needs of the catalyst R&D community, Symyx Technologies developed two microreactor systems. One product consists of 12 or more concentric microreactors in plug-flow configuration machined into a cylindrical metal block. A second offering was made with Argonaut Technologies to commercialize Symyx's Endeavor eight-cell, continuous-stirred parallel pressure reactor that was introduced by Symyx in 1999 (115). The Endeavor was the first multireactor platform for running catalyst reactions either in solution or suspension with input of reagents and output of samples during runs. The Endeavor holds eight 15-mL reaction vessels offering individual control on temperature (up to 200°C) and pressure (500 psi) conditions with various mixing options.

Other manufacturers provide multireactor systems with automation. Altimira Instruments (formerly Zeton-Altimira) introduced the "Celero" automated reactor manifold for the chemical, environmental, and other industries for high throughput screening of catalysts. Chemspeed Ltd. (Switzerland) offers a line of Manual Synthesis Workstations and Automated Synthesis Workstations (ASW) based on a Gilson sample processor platform that can hold up to 6 syringes for liquid handling. The ASW can deliver reagents while shaking, heating, or cooling (−70°−150°C). These workstations are adapted in the factory for use at elevated temperature and pressure for screening of homogeneous catalysts (116).

Beginning in the late 1970s, parallel plug-flow reactors were used for heterogeneous catalyst testing by several researchers (83), however, substantial growth emerged in the late 1990s as high throughput screening of catalysts became of interest to manufacturers of pharmaceutical intermediates (118).

A 49-channel parallel reactor for the high throughput screening of heterogeneous catalysts has been developed by the German firm hte GmbH (Heidelberg and San Diego) (119). The reactor consists of a stainless steel body connected to a multiport valve via capillary tubes. Almost any technique can be used for product analysis, eg, gas chromatography−mass spectroscopy (GC−MS). The reactor has been shown to give data of a quality nearly that obtained from a conventional single-tube plug-flow reactor. This reactor can achieve a test throughput of 49 samples per day.

Claus and co-workers (120) reported studies on the reproducibility of miniaturized screening systems for heterogeneous catalysts. The group studied two different reactor configurations with different degrees of miniaturization for gas-phase reactions: a monolithic reactor system and a system based on MRT. In both cases, a scanning mass spectrometer analyzed for conversion in three reactions, the oxidation of methane, the oxidation of CO, and the oxidative dehydrogenation of *i*-butane.

Most catalyst screening devices are based on small plug-flow reactors. UOP LLC patented a novel miniature fluid bed reactor useful for screening multiple heterogeneous catalysts in parallel (121) as well as process development of catalysts for hydrotreating and hydrocracking using countercurrent flow reactors in parallel (122).

In addition to the fabrication of catalyst libraries based on the types of metals, research has also focused on the fabrication of libraries of support materials for heterogeneous catalysts. Zeolite synthesis requires demanding conditions: temperatures above the normal boiling point of the solvent, high pressures, and high pH. Akporiaye and co-workers reported in 1998 the parallel synthesis and crystallization of 100 zeolite samples that were subsequently analyzed by conventional X-ray diffraction techniques (123). Since that time, SINTEF and UOP LLC formed an alliance and have reported the automated synthesis of zeolites using HTE methodologies (124).

Bein and co-workers developed a parallel reactor/recrystallizing system having nine or 18 chambers with volumes of either 150 or 300 L in which six blocks can be processed simultaneously. Automatic X-ray diffraction (XRD) and/or SEM are used to characterize the samples (125).

Library Characterization. Optical techniques have proliferated in the parallel characterization of HTE libraries since the human eye, or CCD electronics, can quickly detect colors and patterns. Basically, reactants were placed into multiwell plates containing catalysts supported on polymer beads. Using a variety of optical techniques such as fluorescence or thermography, those catalysts having highest activity could be identified. This method was a "parallel analysis", and in some cases faster than other serial techniques, and it served as a proof-of-concept that catalyst libraries could be screened in parallel.

One of the earliest examples of optical screening was in the use of thermography at ir-frequencies. Detection of catalyst activity can take advantage of optical emissions from exothermic reactions. In a typical experiment, a catalyst is placed into a solution containing the reactants. A charged coupled device (CCD) or other ir sensor records the evolution of heat coming from the beads (after subtracting background or latent emissions). One can subsequently determine which of the beads was most active by correlating the position of the beads to the thermal signature (126–128). The methodology has been applied to heterogeneous catalysts and to homogeneous catalysts that have been attached to a support.

Fourier transform infrared imaging (FTIR) has also been used for characterization of heterogeneous catalyst libraries. FTIR imaging combines the chemical specificity and high sensitivity of ir spectroscopy with the ability to rapidly analyze multiple samples simultaneously. FTIR spectrometers require much shorter scan times with equal or better data quality than scanning instruments (129).

Fluorescence has also been used to screen for catalyst activity. For example, Hoveya reported the simultaneous labeling of beads with a fluorescent sensor. The active catalysts are observed with a spectrometer (130). Orschel and co-workers reported the use of laser-induced fluorescence imaging for naphthalene oxidation in 15-member libraries of heterogeneous catalysts. Laser ablation inductively coupled plasma mass spectrometry (ICPMS) was used to confirm the composition of individual samples from the libraries (131).

Senkan and co-workers pioneered the use of resonance enhanced multiphoton ionization (REMPI) for the high throughput testing of catalysts libraries as well as array microreactors (132). Impregnated support pellets were evaluated in a parallel array of microreactors in which the effluent was evaluated using mass spectrometry during laser irradiation. The technique involves the selective photoionization of reaction products over spatially addressable catalyst cluster rows using tunable ultraviolet (uv) lasers under REMPI conditions, followed by the detection of photoelectrons by an array of microelectrodes.

Electrochemical catalysts have been screened using HTE methods. Mallouk and co-workers used fluorescent acid-base indicators to optically detect activity in a 645-member array testing the electrooxidation of methanol. Subsequent screening indicated that a quaternary catalyst, 44% platinum/41% ruthenium/10% osmium/5% iridium, was significantly more active than a traditional binary

50:50 platinum/ruthenium in a direct methanol fuel cell operating at 60°C, even though the latter catalyst had about twice the surface area of the former (133).

High-throughput synthesis and screening of mixed-metal oxide libraries for ethane oxidative dehydrogenation to ethylene have been developed by researchers at Symyx Technologies. A catalyst library was prepared on a 15-cm quartz wafer using vacuum deposition, and the product gases from each sample were sequentially exposed to ethane and scanned using a probe that led to a photo thermal deflection spectrometer and a mass spectrometer. The researchers observed that a ternary Cr-Al-Nb oxide was most active if it contains $\sim$4% Nb (134).

Reetz reported the use of two linked gas chromatography instruments for the high throughput screening of catalysts based on enantioselectivity. Reported in the literature are several examples, including the combination of high-performance liquid chromatography (HPLC), uv/vis spectroscopy and circular dichroism (CD). Analyses of both enzyme- and transition metal-catalyzed reactions have been reported (135).

4. Polymeric Materials

As applied to polymeric materials research, combinatorial, or HTE, methodologies allow efficient characterization of polymer properties and optimization of polymer processing parameters in addition to synthesis of new polymers and accelerated development of new materials. This approach has led to scientific discoveries related to polymer material properties. Consequently, a new feature for polymer materials is that combinatorial and high throughput methods are rapidly extending knowledge discovery into fundamental polymer science as well as industrially important application areas like organic light emitting diodes and coatings.

4.1. Application Areas and Needs. Fundamental characterization of polymers is driven by their applications in structural materials, packaging, microelectronics, coatings, bioengineering, and nanotechnology. Current trends in advanced materials for such applications demand finer control of chemistry, polymer interfaces, morphology, surface properties, multicomponent mixtures, composites, and thin films. Polymeric systems are complex due to phase transitions, reactions, transport behavior, and interfacial phenomena that occur during synthesis and processing. In addition, a large number of variables control these phenomena, including structure, composition, solvent, temperature, annealing history, pressure, and thickness. Conventional microscopy, spectroscopy, and analytical tools for polymer characterization were designed for detailed characterization over a limited set of variable combinations. This approach can be used to test hypotheses efficiently if the most relevant variable combinations are known a priori or can be predicted from theory. However, the complex phenomena and large variable spaces present in multicomponent, multiphase, and interfacial regions in polymers strain the capabilities of conventional one-sample for one-measurement polymer characterization. Hence, the need to develop high throughput techniques for efficient synthesis and characterization of complex polymeric systems. For polymers, the advantages of high throughput methods include efficient characterization of novel regimes of thermodynamic and kinetic behavior, rapid testing and identification of structure–property relationships, testing hypotheses for accelerated development of functional materials, and reduced experimental variance (many measurements at same environmental conditions). High throughput screening has been successfully used for measurements of phase behavior in polymer blend, block copolymer ordering, polymer dewetting, polymer crystallization and organic light emitting devices (OLED).

4.2. Methodologies and Techniques. There has been an increasing effort to apply HTE to materials science, indicated by recent reports of high throughput approaches to developing and characterizing a wide range of inorganic (135–145) and organic/polymeric materials (144,146–156).Unfortunately, the widespread adaptation of HTE to polymers research has been hindered by a lack of techniques for preparing polymer libraries with systematically varied composition (Φ) thickness (h), and processing conditions, eg, temperature (T). In addition, much of polymer characterization instrumentation is not suitable for high throughput screening. For this reason, a number of research groups have begun developing library preparation and screening approaches suited for polymer characterization. This article reviews these recent developments in polymer library preparation and high throughput screening methods. Several novel methods are presented below for the preparation of polymer film libraries with continuous gradients in T, h, and surface energy (E). By focusing on characterization, we have omitted discussion of the many successful examples of high throughput synthesis, experimental design, and informatics previously developed for polymers. These encompass a large variety of materials including biodegradable polymers (146,147,151) support materials for organic synthesis, (150) chemical sensors (148,152) and dendrimers (149). The reader is referred to other sources for a review of these topics (144,157).

Library Fabrication. Techniques have been developed at the National Institute of Standards and Technology (NIST) for preparing continuous gradient polymer libraries with controlled variations in temperature, composition, thickness, and substrate surface energy (155,156,158). These libraries are then used to characterize fundamental properties including polymer blend phase behavior, thin-film dewetting, block copolymer order–disorder transitions, and polymer crystallization. In contrast to the discrete libraries used in pharmaceutical, catalysis, and many inorganic HTE approaches, the deposition of films with continuous gradients in Φ, h, T, and E is a convenient and elegant method for preparing polymer high throughput libraries.

Thickness Gradient Libraries. A velocity-gradient knife coater (155,156, 158) depicted in Figure 6, was developed to prepare coatings and thin films containing continuous thickness gradients. A polymer solution is spread under a knife-edge onto a substrate at constant acceleration. The velocity-gradient results in dried films with controllable thickness gradients. By using several h-gradient films with overlapping gradient ranges, thickness-dependent phenomena can be investigated from nanometers to micrometers. Figure 6 shows a photograph of a polymer gradient, in which the h-gradient produces a continuous change in color and brightness of light reflected from the film–substrate interface.

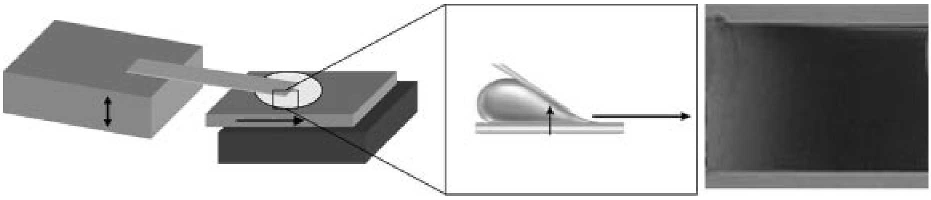

Fig. 6. Schematic of the knife-edge polymer film coating apparatus (left) and a polystyrene coated film with a gradient of film thickness (right).

Composition Gradient Libraries. Three steps are involved in preparing composition gradient films: gradient mixing (Fig. 7**a**), gradient deposition (Fig. 7**b**), and film spreading (Fig. 7**c**), discussed in detail elsewhere (155). Two pumps introduce and withdraw polymer solutions A and B to and from a small mixing vial at rates I and W. Initially loaded with pure B solution, the infusion of solution A causes a time-dependent gradient in composition in the vial. A small amount of this solution is continuously extracted with an automated sample syringe. At the end of the sampling process, the sample syringe contains a solution of polymers A and B with a gradient in composition along the length of the syringe needle. The rates I and W control the slope of the composition gradient, which is linear only if $I = (W + S)/2$ and sample time determines the endpoint composition. The gradient solution (Fig. 7**b**) is deposited as a thin stripe on the substrate, and then spread as a film orthogonal to the composition gradient using a knife-edge coater. The solvent evaporates, resulting in a film with a continuous linear gradient in composition from polymer A to polymer B. Any remaining solvent is removed under vacuum during annealing.

Temperature Gradient Libraries. To explore a large T range, the h- or Φ-gradient films are annealed on a T-gradient heating stage (Fig. 8), with the T-gradient *orthogonal* to the h- or Φ-gradient. This custom aluminum T-gradient stage, described in detail in previous publications (155,157) uses a heat source

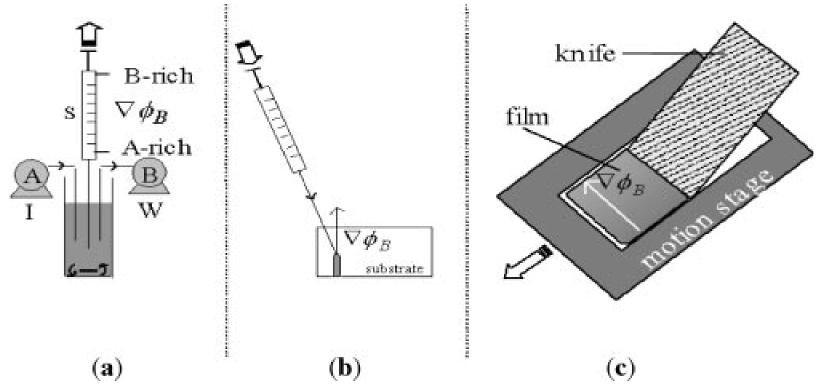

Fig. 7. Schematic of the composition gradient deposition process involving (**a**) gradient mixing, (**b**) deposition of stripe, and (**c**) film spreading. Adapted with permission from Ref. (156).

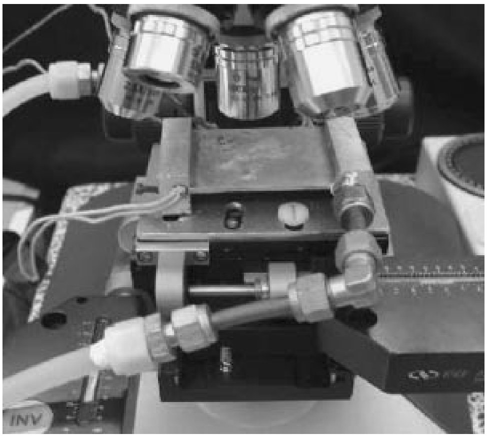

Fig. 8. Picture of the temperature gradient stage for processing of gradient polymer films.

and a heat sink to produce a linear gradient ranging between adjustable end-point temperatures.

End-point temperatures typically range from 160 ± 0.5 to 70.0 ± 0.2°C > 40 mm, but are adjustable within the limits of the heater, cooler, and maximum heat flow through the aluminum plate. To minimize oxidation and convective heat transfer from the substrate, the stage is sealed with an O-ring, glass plate, and vacuum pump. Each two-dimensional T–h or T-Φ parallel library contained ~1800 or 3900 state points, respectively, where a "state point" is defined by the T, h, and Φ variation Δ over the area of a 200 × optical microscope image: $\Delta T = 0.5$°C, $\Delta h = 3$ nm, and $\Delta\Phi = 0.02$. These libraries allow T-, h-, and Φ-dependent phenomena, eg, dewetting, order–disorder, and phase transitions, to be observed *in situ* or postannealing with relevant microscopic and spectroscopic tools.

Surface Energy Gradients. In many polymer coating and thin-film systems, there is considerable interest in studying the film stability, dewetting, and phase behavior as a function of surface energy. A gradient-etching procedure has been developed to produce substrate libraries with surface energy continuously varied from hydrophilic-to-hydrophobic values (159). The gradient-etching procedure involves immersion of a passivated Si–H/Si substrate (Polishing Corporation of America) into a 80°C Piranha solution at a *constant immersion rate*. The Piranha bath etches the Si–H surface and grows an oxide layer, $SiO_x/SiOH$, at a rate dependent on T and the volume fraction H_2SO_4. A gradient in the conversion to hydrophilic $SiO_x/SiOH$ results because one end of the wafer is exposed longer to the Piranha solution (159). Another procedure for varying substrate energy uses composition-gradient self-assembled monolayers (SAMs) (160,161). In this procedure alkane thiolates with different terminal groups, eg, $-CH_3$ and $-COOH$, diffuse from *opposite ends* of a polysaccharide matrix deposited on top of a gold substrate. Diffusion provides for the formation of a SAM with a concentration gradient between the two thiolate species from one end of the substrate to another, resulting in controllable substrate energy gradients.

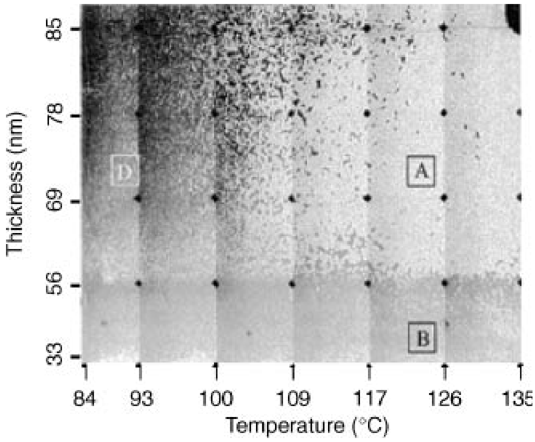

Fig. 9. Picture of water droplets on a uv radiation induced gradient energy SAM surface showing change in droplet spreading due to increasing hydrophobicity from left to right.

More recently, the use of uv radiation to create gradients in surface energy of SAM coated layers (Fig. 9) has been shown to be effective and a convenient methodology for obtaining gradients in surface energy in a controllable manner as compared to the more complicated diffusion approach.

4.3. Characterization of Polymer Library Properties. *Thin-Film Dewetting.* The wetting and dewetting of thin polymer films is of profound importance to advanced materials including microelectronics, optical communications, and nanotechnology. Figure 10 shows a composite of optical microscope images of a T–h library of polystyrene (Goodyear, $M_w = 1900$ g/mol, $M_w/M_n = 1.19$) on a SiO_x/SiOH substrate (162,163).

The thickness ranges from 33 to 90 nm and temperature T ranges from 85 to 135°C. The images (see Fig. 10), taken 2 h after initiation of dewetting, show

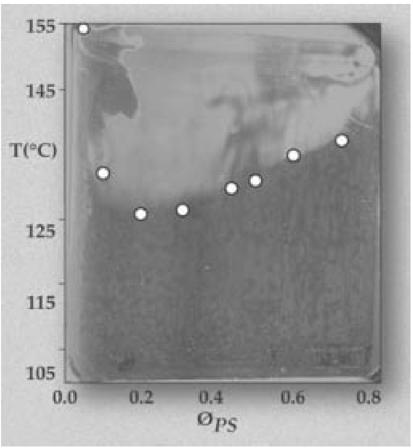

Fig. 10. Composite of optical images of a T–h film dewetting combinatorial library of PS ($M_w = 1800$ g/mol) on silicon, $t = 2$ h.

wetted and dewetted regimes that are visible as dark and bright regions, respectively, to the unaided eye.

Repeated examination of high throughput T–h libraries at thicknesses ranging from (16 to 90 nm) indicates three distinct thickness regimes with different hole nucleation mechanisms. This analysis also allowed the first observation of a T, h superposition for heterogeneous-nucleated dewetting rates, reflecting variations in the film viscosity with T and h.

Phase Behavior. The phase behavior and related microstructure of polymer blends is of critical importance in many engineered plastics, but determination of phase behavior for new blends remains a tedious task. Figure 10 presents a photograph of a temperature-composition library of a polystyrene/polyvinylmethylether (PS/PVME) blend after 16 h of annealing. The lower critical solution temperature (LCST) cloud point curve can be seen with the unaided eye as a diffuse boundary separating one-phase and two-phase regions. Cloud points measured on bulk samples with conventional light scattering (white points) agree well with the cloud point curve observed on the library (20) (Fig. 11). The diffuse nature of the cloud point curve reflects the natural dependence of the microstructure evolution rate on temperature and composition. The high throughput technique employing T–Φ polymer blend libraries allows for rapid and efficient characterization of polymer blend phase behavior (cloud points) in orders of magnitude less time than with conventional light scattering techniques.

Block Copolymer Segregation and Surface Morphology. The morphology of symmetric diblock copolymer thin films has been studied extensively with traditional techniques (164–166). These materials hold potential as templates for nanostructural patterning of surfaces. Because of the thickness dependence in these systems, fundamental investigation of block copolymer segregation is ideal for h-gradient using HTE GMBH methods (157,167). Films of symmetric polystyrene-*b*-poly(methyl methacrylate) (PS-*b*-PMMA) with h-gradients were produced using the knife-edge flow coating technique and annealed at 170°C for 30 h to allow lamellar organization. Figure 12 presents optical micrographs showing morphological changes associated with the addition of two lamellae to the surface of the film as h increases.

Fig. 11. Digital optical photographs of a PS/PVME T–ϕ library after 91 min of annealing, showing the LCST cloud point curve visible to the unaided eye. White circles are conventional light-scattering cloud points measured on separate uniform samples. Picture adapted from cover of *Macromolecules*, 2001.

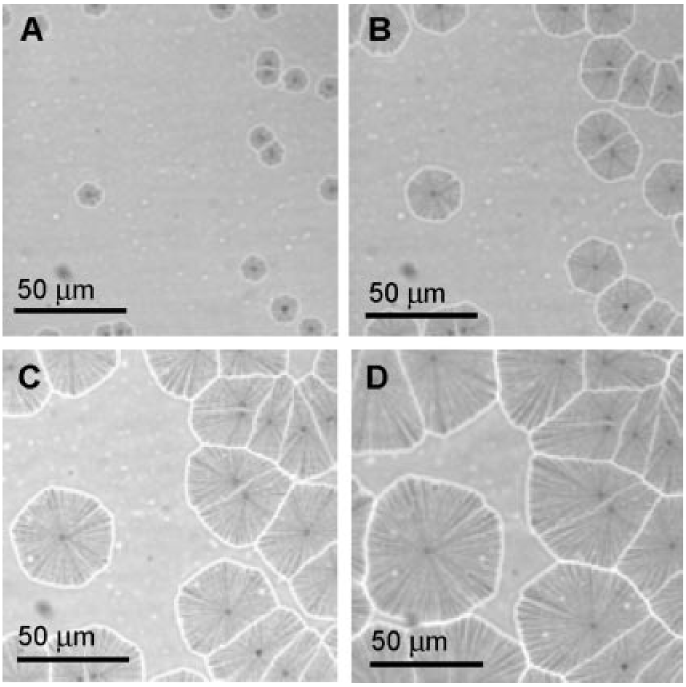

Fig. 12. OM images of block-copolymer lamellae of PS–PMMA cast as a continuous gradient in thickness on a silicon oxide substrate and annealed above its glass temperature (T_g).

This finding is in agreement with previous (non-HTE) work showing that lamellae with thickness equal to the equilibrium bulk lamellar thickness L_o form parallel to the substrate (165–167). The morphology evolves from a smooth film to circular islands to a bicontinuous hole/island region to circular holes back to a smooth film from left to right in the micrograph and repeats twice. This result represents the first observation of stable bicontinuous morphologies in segregating block copolymer thin films (157,168). Another novel observation enabled by HTE methods is the wide thickness range over which the smooth film regions persist.

Polymer Crystallization. Crystal growth rates of isotactic polystyrene were measured as a function of temperature and film thickness on continuous gradient films (Fig. 13).

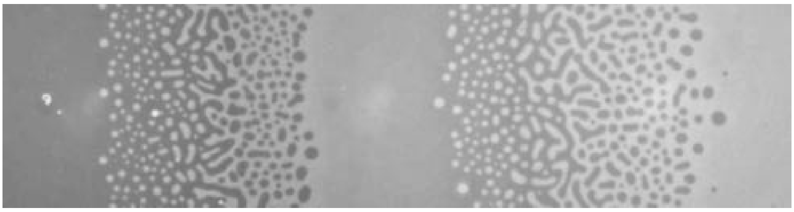

Fig. 13. Optical images of ipS crystallizing at $T = 170°C$.

The measured rates as a function of temperature agree with those obtained previously. A decrease in free energy (G) was also observed in progressively thinner regions of the film below $h = 50$ nm. These results validate the high throughput/high throughput approach to investigating polymer crystallization in thin films, accelerating the pace of experimentation by increasing both the material and processing parameter space available for sampling (168). Furthermore, the dependence of G on h and T was explored in two dimensions to a degree previously considered unfeasible.

Organic Light-Emitting Diodes. Here, we mention two characterization studies of the optimization of organic light emitting diodes (OLEDs). Schmitz and co-workers (153,169–171) used a masked deposition technique to produce thickness gradients in both the organic hole transport layers and the inorganic electron transport and emitting layer. The OLEDs with single-gradient and orthogonal two-dimensional gradient structures were produced in order to evaluate the effects of the various layer thicknesses on the device efficiency. An optimal thickness for both the hole and electron transporting layers was reported. Likewise Gross and co-workers reported the use of high throughput methods to investigate the performance of doped (oxidized) π-conjugated polymers in OLEDs (154). In these devices, the polymers serve as hole transport layers, but an energy barrier for hole injection exists between the polymeric material and the inorganic anode. By varying the oxidation level of the polymer, this energy barrier can be reduced to lower the device working voltage. The effect of oxidation was studied by electrochemically treating the polymer to create a continuous gradient in the oxidation level of the polymer. A gradient in thickness was created orthogonal to the gradient in oxidation to explore variations of both properties simultaneously. For this reason, this study represents a cross between both high throughput synthesis (oxidation steps) and process characterization (thickness gradient deposition). The gradient libraries were characterized by monitoring the efficiency and onset voltage of OLEDs fabricated on the gradients.

Industrial Polymer Coatings and Technology. A number of reports have been published on application of high-throughput approaches for polymer coatings from the industrial arena. Vratsanos and co-workers (172) describe a high throughput screening approach for latex development in architectural coatings. In this, a highly effecient approach for testing abrasion resistance of formulated paints was designed and built. Optical technology is used to detect wear-through of architectural paints on standard plastic Laneta panels. This automated instrument dispenses scrub media and water as specified and records tge endpoints and the development of abraded areas of multiple samples. Images of the panels can be saved digitally for future use. Good correlation is seen between the endpoints found from standard ASTM testing and those using the approach and technique. Schrot and co-workers (173) also describe HTE materials research to accelerate coatings development. They describe how materials as diverse as catalysts and polymers, to formulations and coatings can be developed using combinatorial methods. However, the transition from high throughput drug screening to materials research requires major changes, eg, fast characterization of bulk properties; mechanical hardness instead of molecular assays; modified parallel reactors that can operate at high temperature and pressure, handling viscous materials, aggressive fluids and fast miniaturized materials synthesis. In a comprehensive and well-illustrated article, Wicks and Bach (174) describe the approaching revolution for coatings science brought in by high throughput screening for formulations. The article summarizes the current situation and practices in coatings laboratories, lessons from the pharma world, current situation in materials science, applications of these (combi, HTE) techniques to coatings science and limitations and applicability of the technology. Chisolm and co-workers (175) describe the development of a "combinatorial factory" capable of preparing and testing over 100 coatings per day and the components of such a factory. These include (*1*) an automated system to prepare liquid coating formulations; (*2*) a novel coating application process capable of making high dimension arrays of coatings of controlled thicknesses; (*3*) curing of the coating arrays either thermally or with uv light; (*4*) testing of the coatings using newly developed high throughput screening methods; and (*5*) a data handling process to quickly identify the most promising coatings produced. Ramsey and co-workers (176) at ORNL have developed lab on a chip that can analyze a volume of liquid 10,000 times or more smaller than that used in a conventional analytical instrument. In the lab chips, molecules rather than electrons flow through labyrinths of tiny channels and chambers outfitted with valves, filters, and pumps. Smaller volumes permit faster mixing because molecules do not have so far to travel. Chemicals in a liquid droplet can be mixed and separated very rapidly. In fact, Ramsey and his co-worker Jacobson separated two species in <1 ms — 100,000 times faster than conventional methods.

5. High Throughput Screening: Inorganic Materials

5.1. Introduction. The use of complex inorganic materials is increasing in advanced electronic, optoelectronic, magnetic, and structural applications. These materials are typically composed of three or more elements and may have a crystalline structure, where atoms are in a periodic arrangement, or an amorphous structure, where atoms have no long-range order. Inorganic materials are used in a variety of forms, including thin films and coatings, bulk masses, and powders. The fabrication processes typically involve a number of variables, such as temperature, pressure and atmosphere. It is necessary to search large composition and process spaces to optimize the properties and structure of an inorganic material for a specific application or to discover a new material. High throughput experimentation (HTE) methods are ideally suited to such searches of multiparameter space.

5.2. Applications. The use of HTE methods to increase the efficiency of materials discovery was first reported by Hanak (177) in 1970. Despite his predictions that these methods could increase research productivity by 750-fold for ternary and higher order systems, the application of combinatorial methods to materials research was not reported again for 25 years. In 1995, Xiang and coworkers (178) demonstrated that known high temperature superconducting compounds could be readily identified using HTE methods. Subsequently, combinatorial studies have been performed on materials for electronic, magnetic, photonic, and structural applications, examples of which are given in Table 12.

Table 12. **Application Areas for HTE Studies of Inorganic Materials**

Application area	Material class	References
electronic devices	superconductor	178
magnetic data storage	magnetoresistive	179
displays	phosphors	180,181
microwave devices	dielectrics	182
memory devices	dielectrics	183,184
photonic devices	semiconductors	185
optical data storage	phase change	186
jet engines	superalloys	187
molecular sieves	microporous	188

5.3. Tools and Methodologies. A number of novel library fabrication and characterization techniques have been developed specifically for HTE studies of inorganic materials. Some tools used in conventional studies have been adapted or modified to increase fabrication or measurement throughput.

Library Fabrication. The primary combinatorial variable in most inorganic libraries is chemical composition; additional processing parameters such as temperature, pressure, and atmosphere may also be varied during library fabrication. The techniques that have been used to synthesize thin film, bulk and powder libraries are summarized in Table 13.

The physical vapor deposition techniques for thin-film library fabrication include sputtering, electron-beam evaporation, pulsed-laser deposition, and laser molecular beam epitaxy. In each of these techniques, material is vaporized from a target or source by a high energy process and is deposited on a substrate. The energy source may be an ion gun, an electron gun, or a laser. Two different types of libraries can be formed by physical vapor deposition methods, depending on whether a codeposition or a sequential deposition approach is employed. During codeposition, material is simultaneously vaporized from two or more sources, resulting in a film with a continuously graded composition, also referred to as a continuous composition spread. A schematic diagram of a codeposition system with three targets is shown in Figure 14.

Codeposited libraries have been fabricated by magnetron sputtering, radiofrequency (rf) sputtering, and electron beam evaporation. Composition-spread libraries have also been synthesized by sequential deposition of layers of differing composition, as illustrated in Figure 15 for a pulsed-laser deposition process.

Here, a linear thickness gradient of material is deposited by moving a shutter across the sample; another target of differing composition is then rotated into the laser beam and the second material is deposited as the shutter traverses the sample; and so on. Two-dimensional shutters have been employed to fabricate more chemically complex libraries (183). The resulting multilayer films are postannealed to homogenize the composition through the film thickness and allow reaction of the constituents. Uniform composition films can be formed without postannealing by depositing layers of submonolayer thickness sequentially in a rotating target pulsed-laser deposition system (200). Libraries composed of arrays of cells, each with a discrete composition, have been fabricated by a

Table 13. **Library Fabrication Techniques for Inorganic Materials**

Material form	Fabrication method	Material system	References
thin film	sputtering (*sequential deposition with masks*)	Mo–Nb	177
		Y–Ba–Cu–O, Bi–Sr–Ca–Cu–O	183
		Li–metal–Co–O	179
		doped oxides	181
		doped Ba–Sr–Ti–O	182
	sputtering (*codeposition*)	Zn–Sn–Ti–O	184
		Hf–Sn–Ti–O	189
		Ge–Sb–Te	186
		Tb–Ni–Fe–Co	190
	electron-beam evaporation (*sequential deposition with masks*)	doped oxides	180
	pulsed laser deposition (*sequential deposition with masks*)	doped Ba–Sr–Ti–O	183
		Ba–Sr–Ca–Ti–O	191
	pulsed-laser deposition (*sequential submonolayer deposition*)	Ba–Sr–Ti–O, Sn–In–Zn–O	184
	laser molecular beam epitaxy (*sequential deposition with masks*)	Ba–Ti–O/Sr–Ti–O superlattices	192,193
		doped ZnO	185
	chemical solution deposition	Pb–Zr–Ti–O	194
bulk	melting or floating zone technique	Al–Co	195
		doped Y_2O_3	195
		SiO_2-based glasses	195
	hydrothermal synthesis	Al–P–O	188
	Diffusion multiple approach	Fe–Ni–Mo	187
		Fe–Cr–Mo–Ni, Ni–Al, Ni–Pt	196
	powder inkjet delivery	doped oxides	197
		CuCeO, LaSrCoO	198
	micropipette solution deposition	doped oxides	199

sequential deposition process. In this method, one material is deposited at a time through a mask that permits the material to be put down only onto selected regions of the substrate. A second material is then deposited through a different mask, etc for all of the component materials in the library. Sequential deposition with masks has been used in rf sputtering, electron-beam evaporation, pulsed-laser deposition, and laser molecular beam epitaxy. These library films require postannealing for homogenization and reaction.

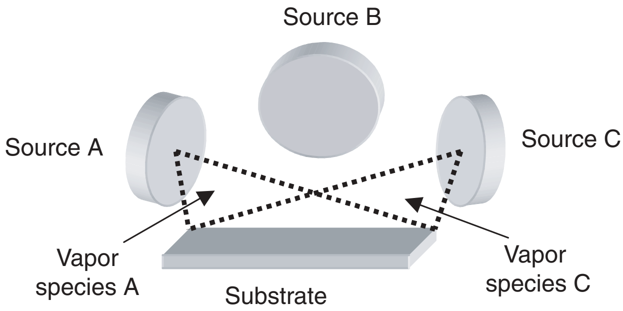

Fig. 14. Schematic diagram of a codeposition system with three sources A, B, and C. The distribution of vapor species from two of the three sources is shown; the concentration of the species from a source is highest at the edge closest to the source and decreases with distance away from the source. The deposited films have a graded composition.

Film libraries composed of discrete cells of differing composition and thickness have also been fabricated by a liquid solution approach. As illustrated in Figure 16, liquid droplets of metallorganic solutions A and B of differing concentrations are dispensed onto a substrate, spun at very high speeds (up to 10,000 rpm) to form thin liquid films, and pyrolyzed to solidify the films.

This sequence can be repeated to build up different thicknesses of films. The array of films must then be annealed to react the constituents.

Two approaches have been used for the synthesis of bulk libraries of continuously graded composition. Both methods involve placing blocks of differing composition in intimate interfacial contact. In the diffusion multiple block method, the blocks are heated to a high temperature to allow thermal inter-

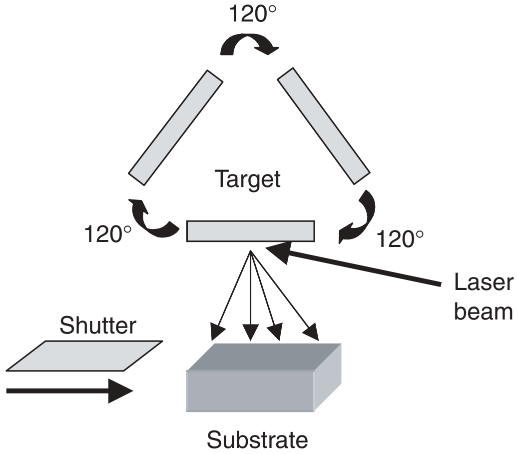

Fig. 15. Schematic diagram of a pulsed-laser deposition system with three rotatable targets and a movable shutter. A linear thickness gradient of material from one target is deposited by moving the shutter across the substrate. Repeating this procedure with the other two targets results in a composition spread film library.

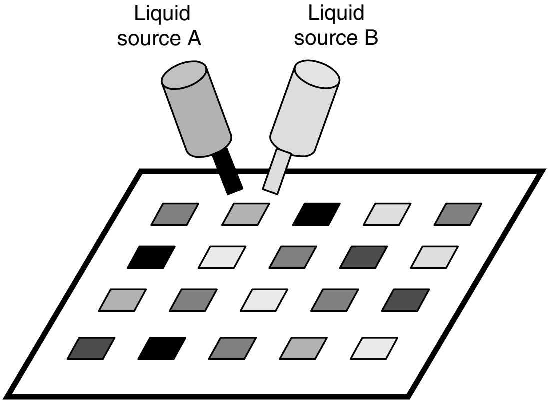

Fig. 16. Schematic diagram of metalorganic liquids A and B being dispensed in differing ratios onto a substrate to fabricate a film library with cells of different compositions.

diffusion; a multiple block composed of four different metals is illustrated in Figure 17.

In the melting or floating zone method shown in Figure 18, the end of one block is heated locally above the melting point; this molten zone is subsequently moved along the length of the block one or more times.

The resulting composition gradient in the solidified block after each pass is determined by the segregation coefficient of each constituent, defined as the ratio of the concentrations of the constituent in the freezing solid and in the molten zone.

Libraries of powders or microporous solids have been fabricated by dispensing liquid reagents into an array of small volume (<0.5 mL) wells via ink-jetting

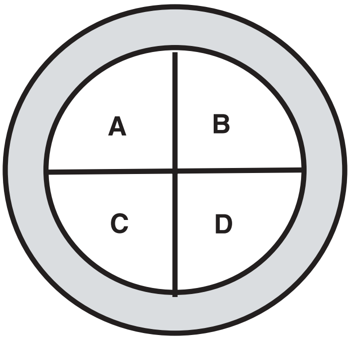

Fig. 17. Top view of a diffusion multiple composition of four materials A, B, C and D. The quarter cylinder pieces of each material are packed into a cylindrical shell and heated to high temperature to cause interdiffusion across the interfaces, thereby producing a composition spread bulk sample. In the diffusion multiple method, the blocks are heated to a high temperature to allow thermal interdiffusion; a multiple composed of four different metals is illustrated.

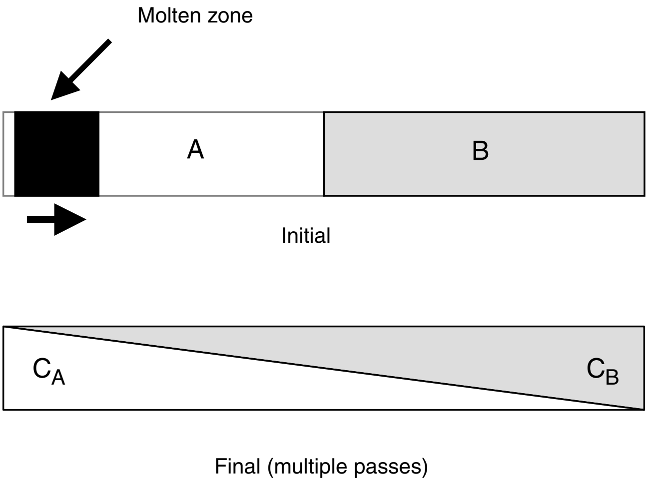

Fig. 18. Illustration of the melting or floating zone method. Two blocks of materials A and B are joined; a small region melted by localized heating is then traversed across the blocks by either moving the block through a stationary heater or by moving the heater over a fixed block. After multiple passes, the two materials mix, resulting in gradients of concentration of A (C_A) and B (C_B) across the block.

or micropipetting processes. An automated scanning multihead inkjet delivery system is shown in Figure 19.

Predetermined amounts of different reagents are dispensed into each well to form an array of samples with systematically varying composition. The library is heated to a low temperature to vaporize the solvent, and then heated at elevated temperatures to promote reaction of the constituents. In an automated hydrothermal method used to synthesize microporous materials, reagents are

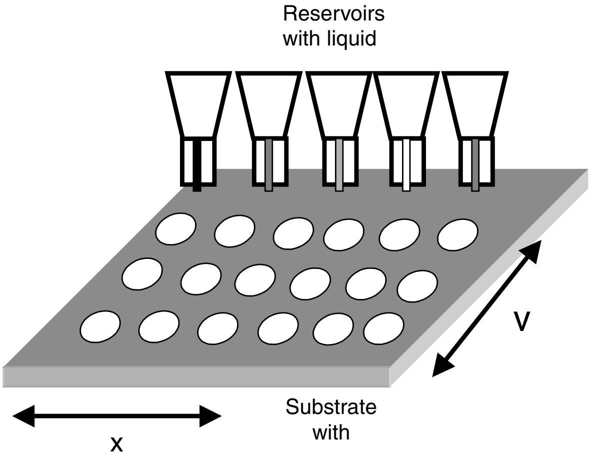

Fig. 19. Schematic diagram of an inkjet delivery system with five reservoirs, each containing a different liquid reagent. Small volumes of each liquid are dispensed into a well with a pump, and the substrate is scanned above the reservoirs in both the x and y directions. The system can be fully automated.

ink-jetted into wells in an autoclave block and processed at elevated temperatures and pressures. The product is washed by filtration and centifuged to remove the liquid.

High Throughput Characterization. Ideally, characterization methods in HTE involve the measurement of a small area or volume of material at a very high measurement rate, or throughput. The measurements may be made sequentially (in serial) or simultaneously (in parallel). In serial mode, one point is measured at a time as the sample is translated on an x–y stage, resulting in an array of data points. In parallel mode, a large area, often the entire sample, is measured simultaneously. Imaging techniques are inherently high throughput since data are collected in parallel from a large area, resulting in a map of information. For any measurement technique, rapid data analysis methods must also be developed to extract the required information from the results. In order to compare the performance of the elements in a given library, it is desirable to formulate a figure of merit that includes the critical properties. For example, the figure of merit for a capacitor application requiring high dielectric constant and high breakdown voltage can be defined as CV_{br}/A, where C/A is the capacitance per unit area and V_{br} is the breakdown voltage (184). For some applications, the figure of merit may simply be one measured parameter, such as resistivity for superconducting materials. Composition and structure of inorganic materials, which often have a strong effect on the properties, must also be determined in library characterization.

Several methods have been used for high throughput electrical measurements. The four-point probe contact technique illustrated in Figure 20 is a common method for measuring electrical resistance (201), particularly for low resistance samples.

In this method, current is applied to a sample through two of the contacts, and the voltage drop is measured across the other two contacts. This four-point configuration eliminates contact resistance, which can dominate electrical

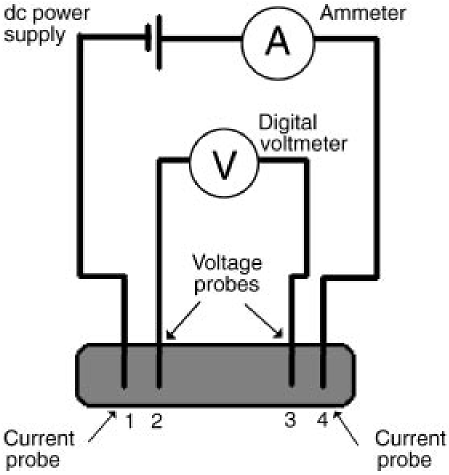

Fig. 20. Conventional four-point contact probe method for electrical resistance measurements. Current is applied across two electrodes (1,4) and voltage is measured across the other two electrodes (2,3).

measurements. A parallel version of this method containing an array of miniature probes was developed to measure the temperature-dependent resistivity in a superconducting film library (178). A similar parallel approach was used to measure resistance as a function of temperature and applied magnetic field in a magnetoresistive film library (179).

Dielectric properties of insulating materials are evaluated by capacitance–voltage measurements (8). One common method for contacting the sample uses a liquid mercury probe as the electrode. A scanning mercury probe technique was developed to measure serially the dielectric constant and breakdown voltage in high permittivity dielectric libraries (184).

Dielectric constant and loss at microwave frequencies can be mapped by a scanning evanescent microwave microscopy technique. This near-field microscopy method provides dielectric information with spatial resolution extending from the microscopic (202) to the atomic scale (203), and has been applied to dielectric thin-film libraries (182). In this technique, microwave radiation is coupled evanescently to the sample surface using a sharp proximal probe that is part of a resonant cavity or a transmission line structure. Analysis of the reflected and transmitted signals yields quantitative dielectric constant and loss maps for a library sample.

High throughput photoluminescence and birefringence measurements have been used to evaluate the optical properties of combinatorial library samples. Photoluminescence is an optical phenomenon resulting from the excitation of an electron to a higher electronic state by the absorption of a photon from a high energy light source, typically a laser (204). Light is emitted when the electron drops back down to a lower electronic state. The emitted light or luminescence has a specific wavelength determined by the energy difference between the two electronic states; thus, the light has high spectral clarity of a specific color, such as red, green or blue. Combinatorial phosphor libraries have been screened for luminescence efficiency and color by a photoluminescence parallel imaging technique (180). In this method, the entire library is illuminated with an ultraviolet lamp, yielding a color intensity map of visible emission that can be quantitatively analyzed using materials with known efficiency as calibration standards. Improved quantitative analysis of the excitation and emission spectra was obtained using a scanning spectrophotometer (205). This technique measures the absorption, transmission, or reflectance of light from a material as a function of wavelength.

Electrooptic measurement methods probe the effect of an electric field on the optical properties of a material (206). A high throughput birefringence technique was developed to measure the electrooptic coefficient, defined as the change in refractive index with applied electric field (207). In this method, a row of parallel electrodes is deposited on a library, and a combination of direct current and alternating current electric fields is applied across each pair of electrodes. The laser light illuminating the sample interacts with the applied electric field, and the two electric components of the light, one parallel to the applied field and one perpendicular to the applied field, are analyzed. The resulting signal is used to calculate the electrooptic coefficients.

X-ray diffraction is commonly used to study the structure of inorganic materials (208). In this technique, the angle of the sample (theta) and the angle of the detector (two-theta) are scanned, and the intensity at each value of two-theta is measured. The resulting data are then used to identify the crystalline phases present in the sample. X-ray fluorescence (208) measurements are used to determine the chemical composition of multicomponent materials. Standards of known composition are measured first for calibration purposes and are used to quantify the composition of an unknown sample. Measuring X-ray diffraction or X-ray fluorescence on a submillimeter area in a combinatorial library requires the use of a microbeam (209) or a microfocusing method, and a high energy X-ray source such as a synchrotron radiation beam to generate sufficiently intense signals for the analysis of small volumes of material.

5.4. Summary. There is a wealth of opportunities for applying HTE methods to inorganic materials. A wide variety of methods have been used to fabricate thin-film, bulk, and powder libraries of varying composition. High throughput characterization tools to measure electrical, optical and structural properties have been developed for inorganic libraries. These fabrication and analysis tools will facilitate the discovery and optimization of multi-component inorganic materials for advanced applications.

6. The Path Forward

6.1. Methodologies. The future of high throughput experimentation (HTE) will require that the basic underlying software technology must be capable of defining profitable experimental spaces; visualizing complex data relationships; and of correlating high throughput experimentation target materials with properties to permit database queries from a broad spectrum of data mining engines and the development of structure–property relationships. This requires interfacing with data visualization tools at the back end and statistical experimental design engines on the front end while remaining compliant with enterprise-wide systems for knowledge management and maintaining control of experimental hardware. The integration of Informatics, Modeling, and Design are high risk opportunities.

Informatics. Integrated packages will need to link modeling, development and management of databases and search engines, hardware control, data visualization, and logistics. More specifically (210):

- Database search engines will need to be interoperable with the diverse flavors of databases currently in use.
- Development of QSPR for materials. The term QSAR is used in organic combinatorial synthesis;
- Acceleration of the design process from atomic level chemistry to engineering design by developing relationships between chemistry, processing, microstructure, etc, and processing involving metastable states, etc.
- Development of a query language for linking many different methods for querying the data with appropriate query optimization methods.
- Assembly of high performance data mining toolboxes that extend database management systems with additional operators.

- Connections to the diverse metrics in materials design, where important properties are sensitive to numerous ranges of length or time scales, eg, from 10^{-9} to 10^{2} m and nanoseconds to years;
- Development of tools to present complex, multidimensional data relationships to the human interface; HTE establishes a new paradigm for the researcher who now must interpret data surfaces and not just data points.

Design of Experiments. Due to the potentially high number of candidates available from combinatorial methodologies, the design of the sample library requires rational chemical synthesis or process information to reduce the number of samples and experiments without increasing the probability for endless searches, false positives, or false negatives.

New tools will have to be developed to enable the integration of information into molecular- and property-modeling engines. The increased amount of data that can be input into computational engines will require a significant increase in speed, bandwidth and storage. Advanced, high speed quantum calculation programs such as Wavefunction, Inc.'s program SPARTAN (211) and Acellrys' (formerly MSI) program Cerius (212) will require interfacing with databases and experimental design programs. Advances in experimental strategy for dealing with large, diverse chemical spaces, using space-filling experimental designs, predictive algorithms, and optimization techniques will be critical.

6.2. Hardware. Micromachines and microreactor technologies (MRT) based on microelectromechanical systems (MEMS) and nanoelectromechanical systems (NEMS) will address the need for higher library densities to facilitate reduced raw materials costs for library fabrication and economies of scale and modularity in laboratory instrumentation. Construction of solid-state libraries currently requires automated deposition onto substrates, using, eg, microjet, laser ablation, vacuum deposition using pulsed vapor deposition (PVD) or chemical vapor deposition (CVD), or microfluidics in a lab-on-chip application. Microscale methods have already been commercialized for health care diagnostics with liquid samples, and this technology will penetrate the CPI and materials arena with systems utilizing solution state reaction substrates with homogeneous catalysts. There is a growth of activity in this area, with links to the HTE community, especially for drug discovery applications.

There is a growing international effort to understand MRT for distributed manufacturing of chemicals and for high throughput screening. Principal components of MRT are analogous to large-scale machines—reagent mixers, reactors, distribution and separation. The key technical challenges for MRT are in component integration, development of modular systems, and development of engineering tools to design and build microscopic systems. Since fluid flow in these devices is laminar, a significant challenge is in understanding fluid dynamics in these systems. Clearly, the convergence of the microelectronics technologies with microreactor technologies will accelerate in the near future, and are being tracked with interest by many parties for their economic potential. The current technology leaders for chemical process development and high throughput screening are the German Institut für Mikrotechnik Mainz (213). Research in the United States is centered primarily at the Pacific Northwest National Laboratory (214) , The Oak Ridge National Laboratory (215) and at the

Massachusetts Institute of Technology Microsystems Technology Laboratory (216). A collaboration between DuPont Experimental Station and Massachusetts Institute of Technology (MIT) has produced a circuit board-level discovery plant containing multiple socket-borne, interchangeable catalytic reactors with integrated fluidics control, heat transfer, separation, and mixing for combinatorial discovery and process development (217). The U.K. Lab on a Chip Consortium

Table 14. **Technology Challenges**

Software	
technology	*challenge*
library design	
statistics modeling	• development of higher order designs
literature/patent databases	• (review by NSF is pending) • query languages; visualization; integration
informatics	
QSPR (structure-property predictions)	• property prediction, large-scale correlations, integration into experimental design tools
database query engines	• new languages, genetic programs • interoperability, enterprise-wide integration
Hardware	
technology	*challenge*
screening	
thermal properties	•electrical and thermal conductivity
optical characterization	• fluorescence, luminescent properties, X-ray diffraction
mechanical properties	• modulus, tensile strength, impact resistance
electrical properties	• capacitance, conductance
chemical properties	• molecular weight • polymer architecture/morphology • catalyst turnover, selectivity, conversion
processing	
control of physical environment	• control of temperature and pressure over library array with control over individual sample sites or wells • sample size—control of interfacial diffusion, mass transport properties, etc
deposition	
thermally driven (e-beam, laser, etc)	• delivery of finite samples or composition spreads of consistent, known composition at microscopic sizes: reproducibility
laser ablation	
microjet	
vacuum deposition	
robotic pipetting of nanoaliquots	• reduction of cross-talk of sample properties through diffusion, etc. across substrate surface
micro-reactor technologies	
systems integration	• development of standards for modular component interconnections • process control devices tuned to MRT • modeling for fluid flow, heat and mass transfer
reactor design	• substrates: glass, polymer, metal
manufacturing processes	• surface micromachining using wet or dry chemical etching, laser ablation, mechanical micromilling, LIGA processes

(218) is a miniaturization research project, which started in early 1999 with government funding of £1.33 million matched by £1.8 million from U.K. industry. Seven universities and twelve companies are participants and, over the next 30 months, will develop and commercialize microdevices for chemical analysis and synthesis (219). Academic and industrial partners will study reactions in an on-chip environment—how do conditions affect reaction efficiency compared with bulk reactions—as well as development of an infrastructure required for the commercial exploitation. Some of the technology challenges are shown in Table 14.

Microscale sensors. High throughput methods will drive the development of advanced sensors and sensor arrays. The current technology relies on contact and noncontact methods of characterization and external control of process conditions. A significant impetus for developing microscale sensors has been the U.S. Department of Defense (220), primarily in response to battlefield detection of chemical and biological warfare agents and portable power generation, and the National Aeronautics and Space Administration (NASA) for microrobotic space exploration. The CPI sector is moving toward smaller, more integrated sensing devices in process control of manufacturing sites. Robotics, next-generation "titer plates", lab-on-a-chip designs, and rapid scanning devices for HTE innovation, likely with application-driven tools targeting specific physical properties that can be analyzed at microscopic levels. Automated library processing is especially challenging for new materials development since samples within a library may require different or nonequilibrium processing parameters across the library. Therefore, with the impetus toward MRT lab-on-chip devices, integration will drive the development of foundry methods to produce on-chip optical sources (eg, semiconductor lasers) as well as detectors. Finally, the capability for interpretating bulk characteristics from microscale will place increasing pressure on computational tools such as QSPR.

Success using HTE in the CPI and materials sectors has already resulted in the reduction of idea-to-commercialization cycle times to 3 to 5 years from 7 to 10 years. HTE has already reached commercial validation.

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Certain commercial equipment, instruments, or materials are identified in this paper in order to specify the experimental procedure adequately. Such identification is not intended to imply recommendation or endorsement by the National Institute of Standards and Technology, nor is it intended to imply that the materials or equipment identified are necessarily the best available for the purpose.

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