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Invited Paper

High throughput methodologies for chemicals and materials RD&E[1]

by

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I. SUMMARY

The U.S. chemical process industry (CPI) has annual revenues over $400 billion and supports the downstream innovations of other critical U.S. industries. Innovations in the chemical process industry support over $1.2 trillion in product sales and service for the downstream value chains. Yet R&D funding within the chemical industry has been relatively flat over the last decade at about $12-14 billion while being focused increasingly on applied research and process development.[2]

Global market pressures are driving the chemicals and advanced materials industries to improve RD&E productivity as measured by return on investment for new products. The principal drivers are reduced cycle times and higher quality at lower cost, with reduced environmental impact. One approach to increased productivity is high throughput research (HT RD&E) (also known as "combinatorial chemistry"), where a convergence of technologies enables a parallel approach to discovery and process development. These methodologies produce "libraries" of new solid-state and soluble materials in a matter of hours and days, rather than months and years, at a fraction of the cost of traditional serial approaches. New materials have already been reported with unique chemical, optical, and electronic properties utilizing a variety of parallel screening approaches.[3]

The CPI and materials industries have indicated a need to accelerate the implementation of this capability in the United States. Industry has indicated that the Advanced Technology Program (ATP) of the National Institute of Standards and Technology (NIST) can facilitate the emergence of new technologies. The ATP can spur the fusion of these new technologies for subsequent diffusion to other areas. It can facilitate the integration of complex systems; the ATP can help the integration of otherwise diverse technologies; and the ATP can reduce the cost of implementing high throughput RD&E so that more R&D cost-sensitive industrial sectors will be able to invest in this new capability earlier. This position paper is a response to industry's interest in the development of a portfolio of projects in the ATP to fund methodology development in the area of high throughput RD&E for advanced materials (catalysts and biocatalysts, polymers and polymer blends, electronic materials, biomaterials, etc.) that could accelerate the building of synergies, promote inter-industry developments, and counter significant foreign competition in the CPI and materials sectors.

The ATP has responded to the need[4] of industry for Federal Government investment in this area by awarding three project proposals from the FY 1999 Open Competition that competed successfully against the ATP Selection Criteria. These projects are attempting to develop breakthrough technologies for applications in polymer coatings and heterogeneous catalysts. The need for further growth has been expressed, and the ATP continues to encourage applications for funding in future Open Competitions in the area of high throughput methods for RD&E of chemicals and materials, as well as other high technical risk areas that have the potential for broad economic benefit for the nation.

This report is a collection point for non-proprietary business and technical information gleaned from industry input, for example as obtained at an Industry Probe Working Group Discussion held in March, 1998, public ATP Workshops held November 18, 1998 in Atlanta, GA, November 16, 1999 in San Jose, CA, as well as ATP's participation in many industrial forums in the last two years. Complete review articles can be found in the references.

Keywords: combinatorial chemistry, combinatorial methods, high throughput screening

In *Combinatorial and Composition Spread Techniques in Materials and Device Development*, Ghassan E. Jabbour, Editor, Proceedings of SPIE Vol. 3941 (2000) • 0277-786X/00/$15.00

II. THE ATP PROCESS

The goal of the ATP is economic growth and the good jobs and quality of life that come with economic growth. ATP awards are made strictly on the basis of rigorous peer-reviewed competitions designed to select the proposals that are best qualified in terms of the technological ideas, the potential economic benefits to the nation (not just the applicant), and the strength of the plan for eventual commercialization of the results. The ATP protects the confidentiality of documents submitted by industry as required by the ATP statute. The ATP does not fund projects that are predominantly basic research or product development. The ATP submits all proposals to peer review by following the process outlined in Figure 1.

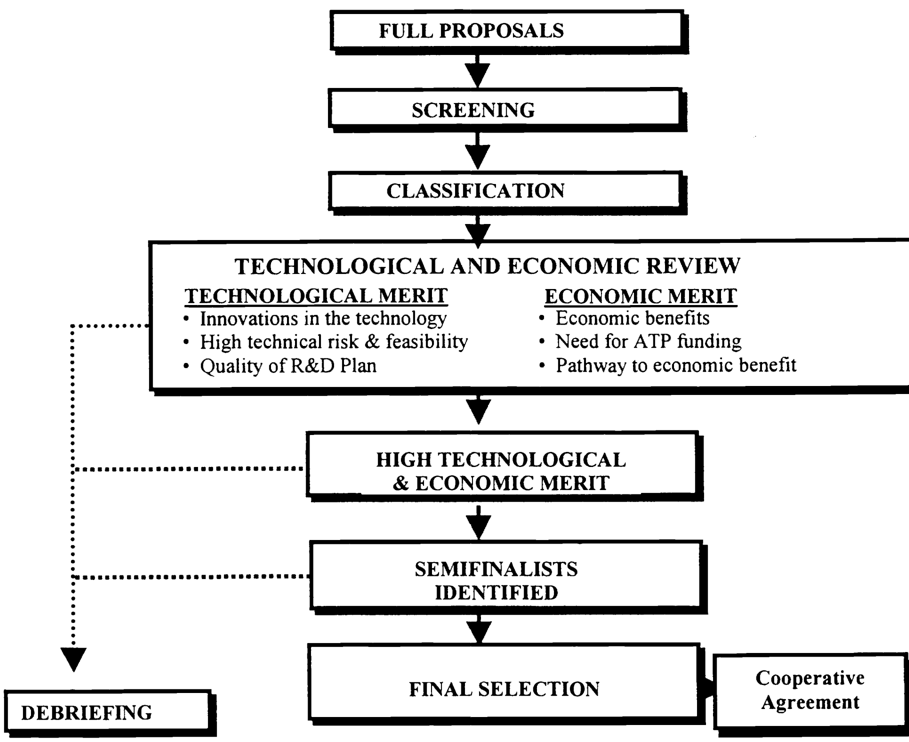

FIGURE 1. THE ATP SELECTION PROCESS

Non-proprietary white papers (not proposals) submitted by industry, academia, and government facilities might outline a specific opportunity area and describe the potential for U.S. economic benefit, the technical ideas available to be exploited, the strength of industry commitment to the work, and the reasons why ATP funding is necessary to achieve well-defined research and business goals. These position papers contain no proprietary information and state as succinctly as possible the goals of a proposed technology challenge that needs the benefit of a cluster of synergistic projects to maximize benefit to the nation's economy.

ATP project proposals and optional pre-proposals submitted to ATP are evaluated against the scientific and technical merit of the proposal and the potential for broad-based economic benefits to the United States. A fifty-percent weighting applies to the scientific and technological merits of the proposals: innovations in the technology; high technical risk and feasibility; and quality of the research plan. A fifty-percent weighting is applied to the economic merits of the proposals: economic benefits; the pathway to economic benefit; and need for ATP funding. Overall, proposals are ranked competitively according to the six components of the two Selection Criteria as expressed in the written proposal.

Optional pre-proposals may be submitted year-round and provide a mechanism to receive written feedback on the strengths and weaknesses of the project plan and on how to improve the competitive potential of a subsequent full proposal. Applicants are strongly urged to initiate proposal preparations early and to follow instructions carefully. Proposal Preparation Kits for each new competition are distributed via the ATP Mailing List (telephone 1-800-ATP-FUND to register) and on the ATP internet world wide web site http://www.atp.nist.gov/atp/apply.htm.

III. PROBLEM STATEMENT

Major forces—globalization of markets and the pace of technological change—continue to drive private sector R&D to more focused, shorter-term investments to maximize near-term returns to the shareholders. Increased pressure on manufacturers to produce "faster/lower-cost/better" has increased the demand for new products made from new materials and/or utilizing new processes while utilizing more environmentally-friendly materials and processes. In order to achieve these goals, the CPI and materials sectors are expected to follow a trend occurring in other technology sectors and will focus on core business areas with greater dependence on strategic partnerships. The move to outsource research and development efforts to outside firms (the "discovery and development industry") and/or create facilities in countries with lower-cost labor is an emerging business model in the CPI and materials sectors.

During the 1990's, the pharmaceutical industry responded to market pressures (product launch times, return on R&D investment, large revenues for blockbuster drugs, reduced profits from health management organizations, etc.) by switching from serial discovery processes for generating and analyzing drug targets to using "combinatorial chemistry" research methods. This methodology can qualify a large number (a "library") of possible candidates ("hits" from primary screening, "leads" from secondary screening); in 1999, the ability to screen 1 million distinct compounds per year was realized in the pharmaceutical discovery process, with R&D costs per lead dropping approximately two orders of magnitude. The capability to convert traditional discovery processes to an "assembly line" was facilitated by the convergence of several technologies applied to a well-defined market opportunity: computer software (data bases, molecular modeling, machine control software, and statistics); more cost-effective high-speed computers; robotics; MEMS (micro-electromechanical systems) technologies; and sensors.

Figure 2 illustrates how one can differentiate the key steps of a typical high throughput RD&E process:
Target Definition utilizing expert opinion, hypothesis, and computer modeling;
Library Design with computational inputs such as quantitative structure-property relationships (QSPR), and molecular modeling. Design of Experiments (DOE) is required to reduce the number of samples that will be necessary to define sample spaces within the experimental universe or to direct screening to other spaces within the universe;
Library Fabrication involves the automated deposition and/or processing of an n-dimensional matrix of physical samples;
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;
Data Collection and Analysis using the data-base and artificial intelligence tools—"informatics"—expanded into the more complex realm of materials properties.

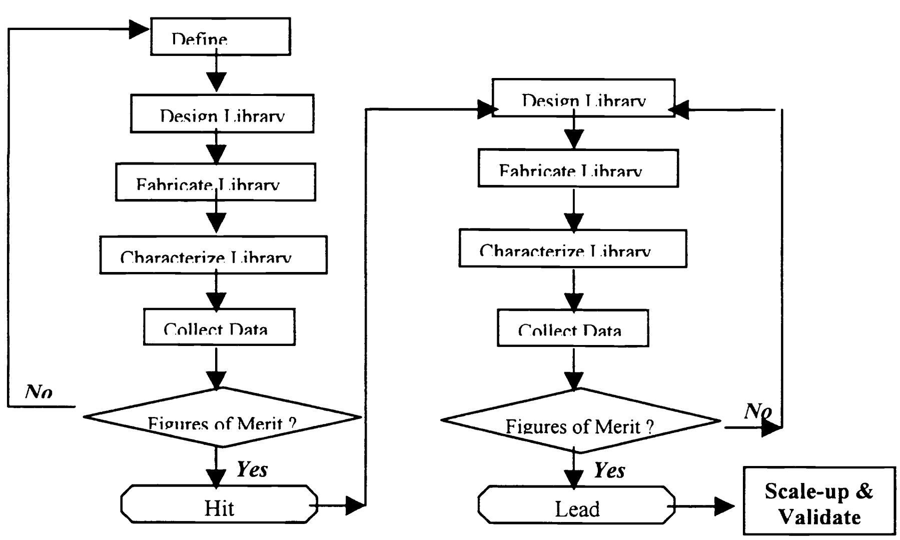

Figure 2. The High throughput Process Flow

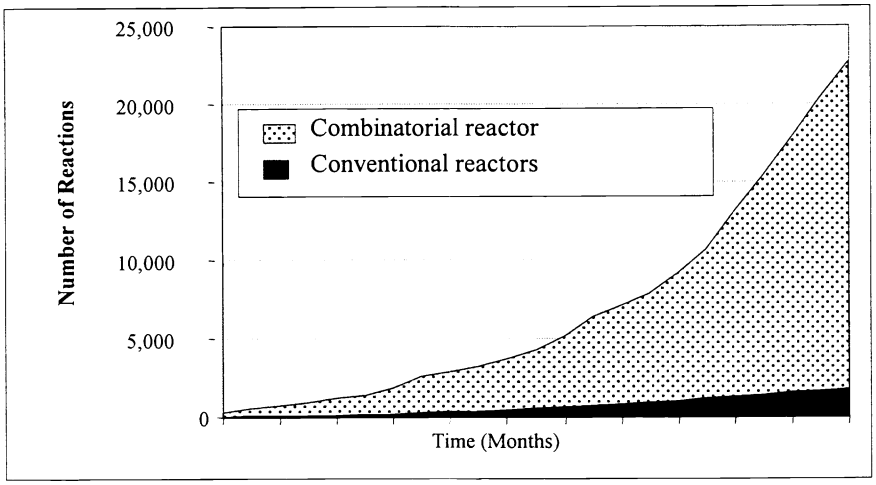

FIGURE 3. COMBINATORIAL VS. CONVENTIONAL REACTOR THROUGHPUT[5]

Industrial sectors other than the pharmaceutical industry recognized the attributes of the new drug discovery paradigm and are implementing high throughput screening of new materials. Serial discovery processes rely on the preparation and characterization of individual samples from bench scale (mg. or grams) to pilot scale (grams to kilograms). Parallel, HT methods can perform the same preparation and characterization using automated laboratory instrumentation. As shown in Figure 3, there are expectations that HT screening can significantly accelerate the discovery of new catalysts. An emerging trend is to continue the parallel process flow into the process and product development stages to realize substantial increases in the number of samples that can be analyzed.

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 technology spill-over from drug discovery has resulted in the development of high throughput (HT) methodologies for inorganic materials and fine and specialty chemicals and materials. Because HT techniques are especially suited to complex mixtures containing many different components and/or processing conditions, this methodology lends itself to the discovery of new advanced materials that are gaining performance through the use of multi-component formulations, for example the addition of dopants to electronic materials or polymer blends for engineering plastics. In addition, HT RD&E permits the screening of compositions that would not otherwise be attempted, that is, it maximizes serendipity. For example, Symyx Technologies Inc.[6] has 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''). Applications beyond catalysts have been explored, for example phosphors, thermoelectric materials, and optoelectronic devices such as ZnO-based compound semiconductors for light-emitting diodes (LEDs).[7]

In the pharmaceutical industry, new drug candidate molecules are tested for biological activity by chemical means such as gas chromatography, nuclear magnetic resonance spectrometry, mass spectroscopy, fluorescence spectroscopy, or the response of a biochemical receptor. Advanced materials, on the other hand, require performance-based characterization that is often application-specific. For example, selectivity and conversion analysis for a matrix of heterogeneous catalyst formulations will require the development of sensors for sampling the product/reactant mixtures produced by the catalyst lead sample array, not just an analysis for elemental composition or molecular activity.

Materials processing typically involves more energetic reaction environments than pharmaceutical processing, with temperature and pressure requirements as high as several hundred degrees and hundreds of Pascals. Micro-scale solid state samples may also be subject to significant influence from the substrate onto which they are deposited--interfacial effects can produce phenomena that are not reproducible in bulk samples of manufacturing scale. Thus, advanced materials suffer from "scalability", or differences in micro-scale to lab- or pilot-scale properties. Finally, 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.

The leverage of tools developed for drug discovery, e.g., activity-focused/solution-state systems, to solid state materials is challenging due to the diversity of potential design, fabrication, and analysis parameters. Some of these challenges are shown in Table 1.

TABLE 1. DRUG DISCOVERY TARGETS VS. SOLID STATE TARGETS

Drug Discovery	*vs.*	**Solid State Materials**
• Discrete molecules of C, H, F, N, O, P		• Extended structures of many elements potentially in metastable states
• Finite number of active sites, can be characterized and modeled computationally		• Ill-defined distribution of active sites and structures
• Purity >85%; parallel purification techniques employed before characterization		• "Pure" solids are meaningless especially with small samples having interfacial effects with the library substrate
• Structures reproducible (*a priori*)		• Reproducible structures difficult, if not impossible, to create *a priori*
• Chemical characterization, biological activity well developed for rapid or parallel methods		• Characterization of multiple independent properties and composition not straightforward
• Descriptors for diversity		• Few or no ideas exist about how to do it
• Registration of library samples straightforward		• Few or no ideas exist about how to do it
• Synthetic building blocks available		• A few building blocks available

IV. TECHNOLOGY CHALLENGES

Information gained from the many public discussions[8] in this area has been supplemented by additional input in the form of non-proprietary position papers submitted to the ATP by industry. In addition to identifying key areas of technology development and application areas, these data describe the technical and commercial barriers to implementing this methodology in the global CPI and materials sectors.

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 is to have high-throughput research become part of expanded enterprise-wide systems that include tools for hardware interfaces, technology assessment/decision, and logistics. Because HT RD&E is currently highly capital intensive, with start-up costs in the range of \$8M to \$20M,[9] 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.

A. SOFTWARE

The basic underlying software technology must be capable of defining profitable experimental spaces and visualization of complex data relationships, and of correlating 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 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 overall view of software integration is shown in Figure 4, where the integration of Informatics, Modeling, and Design are high-risk opportunities.

- *Informatics*. Integrated packages linking modeling, development and management of databases and search engines, hardware control, data visualization, and logistics. Data base search engines will need to be interoperable with the diverse flavors of databases currently in use;

- Development of Quantitative Structure Property Relationships (QSPR) for materials. The term Quantitative Structure Activity Relationships (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 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, for example from 10^{-9} m. to 10^{2} m. and nanoseconds to years;
- Development of tools to present complex, multi-dimensional data relationships to the human interface. HT RD&E establishes the 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 in HT 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[10] and MSI's program Cerius[11] 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.

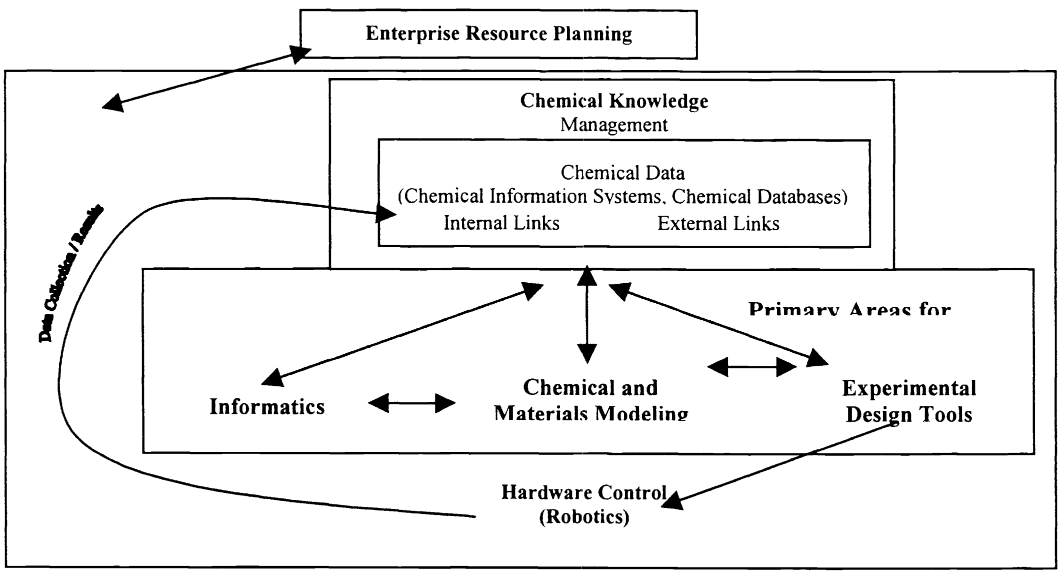

FIGURE 4. THE INTEGRATION OF SOFTWARE SYSTEMS

B. HARDWARE

The basic underlying hardware technologies needed for HT library fabrication and analysis are enabling and emerging technologies that are finding applications in other arenas. Broad technical needs have been identified by industry (Table 2).

- Increasing computer throughput with, for example, massively parallel computers and high bandwidth networks;

- Micro-machines and micro-reactor technologies (MRT) based on micro-electromechanical systems (MEMS) 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 materials libraries currently requires automated onto substrates, using, for example, micro jet, laser ablation, vacuum deposition (PVD, CVD), or micro-fluidics in a lab-on-chip application. Micro-scale methods have already been commercialized for health care diagnostics with liquid samples. Preliminary market penetration in the CPI and materials arena will be with systems utilizing solution state reaction systems using homogeneous catalysts.

- There is an growth of activity in this area, with links to the HT RD&E community, especially for drug discovery applications.[12] One prototype microreactor is shown in Figure 5.[13] 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 micro-reactor 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[14], and Forschungszentrum Karlsruhe.[15] Research in the United States is centered primarily at the Pacific Northwest National Laboratory[16] and at the Massachusetts Institute of Technology Microsystems Technology Laboratory.[17] 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 HT discovery and process development.[18]

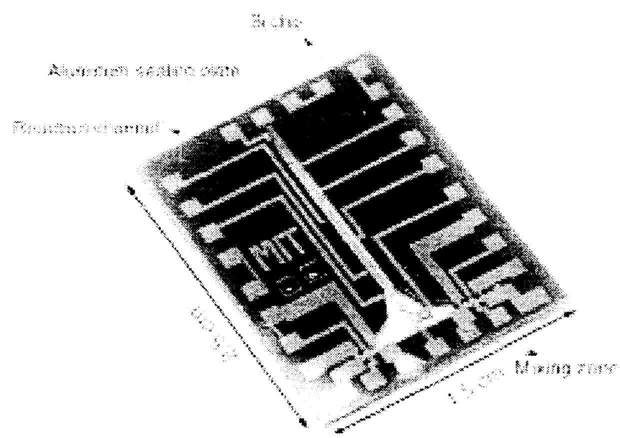

FIGURE 5. PROTOTYPE MICRO-REACTOR FOR FLUIDIC SYSTEMS FROM MIT

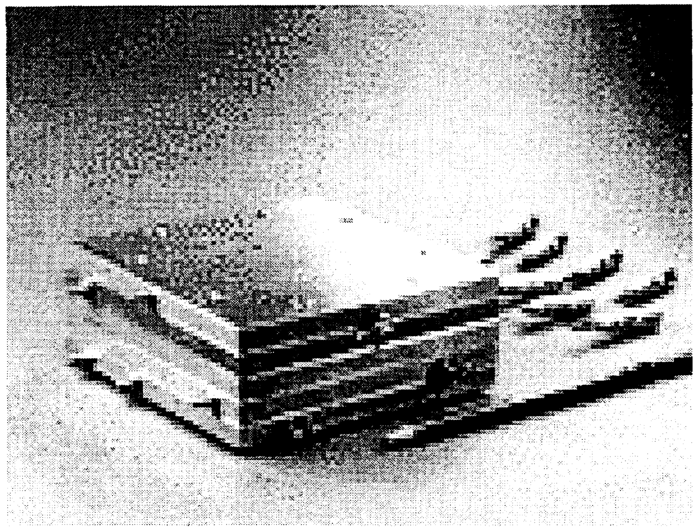

FIGURE 6. MICROREACTOR ASSEMBLY FROM THE INSTITUT FÜR MIKROTECHNIK MAINZ

- Micro-scale sensors. High throughput methods will drive the development of advanced sensors and sensor arrays. The current technology relies on contact and non-contact methods of characterization and external control of process conditions. A significant impetus for developing micro-scale sensors has been the U.S. Department of Defense,[19] primarily in response to battlefield detection of chemical and biological warfare agents and portable power generation, and from National Aeronautics and Space Administration (NASA) for micro-robotic 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 HT materials innovation will be 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 non-equilibrium 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 (e.g., semi-conductor lasers) as well as detectors. Finally, the capability for interpretation to bulk characteristics from micro-scale will place increasing pressure on computational tools such as QSPR.

TABLE 2: TECHNOLOGY CHALLENGES

SOFTWARE	
Technology	**Challenge**
Library Design	
Statistics	- Development of higher-order designs
Modeling	- (Review by NSF is pending)
Literature/Patent Databases	- 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 - Inter-operability, enterprise-wide integration

Hardware	
Technology	**Challenge**
Screening Thermal properties Optical Characterization Mechanical Properties Electrical Properties Chemical Properties	2-dimensional or parallel sensors for: - Electrical and Thermal Conductivity - Fluorescence, luminescent properties - Modulus, Tensile Strength, Impact resistance - Molecular Weight - Polymer architecture/morphology - Catalyst Turn-over, 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.) Laser ablation Micro jet Vacuum Deposition Robotic pipetting of nano-aloquots	- Delivery of finite samples or composition spreads of consistent, known composition at microscopic sizes: reproducibility. - Reduction of cross-talk of sample properties through diffusion, etc. across substrate surface
Micro-Reactor Technologies Systems integration Reactor design Manufacturing processes:	- Development of standards for modular component interconnections - Process control devices tuned to MRT - Modeling for fluid flow, heat and mass transfer; - Substrates: glass, polymer, metal - Surface micro-machining using wet or dry chemical etching, laser ablation, mechanical micro-milling, LIGA processes.

V. PROBLEM STATEMENT

The two major technological hurdles are systems integration of the hardware and software tools, and the scalability of micro-scale results to end-use scale.

A. SYSTEMS INTEGRATION

The transfer of traditional *serial* research methodologies to multi-dimensional *parallel* methodologies will require the integration of previously diverse computational and characterization tools for sample library design, sample library fabrication, characterization, and informatics.

B. SCALABILITY

The ability to utilize data obtained from libraries of micro-scale samples will require scientific advances in the areas of interfacial effects and structure-property relationships.

C. COMMERCIAL CHALLENGES

The major commercial hurdle is validation that HT RD&E methodologies lead to increased productivity, for example in terms of increased return on investment (ROI) and higher net present value (NPV) for new products. Time-based competition is driving many industries to increase R&D funding at the expense of reducing allocations to capital assets. The “new economy” may bring about the acceptance of new metrics, for example the rate of RD&E expenditures vs. the rate of capital investment in manufacturing assets.[20] In addition, the concept of intellectual property as a valued asset is becoming more widespread as enterprise-wide knowledge management becomes increasingly viable.

There is a resistance to believe that HT discovery and process development methodologies will impact R&D productivity in most firms. Large capital investments will be made only by the few large companies that can guarantee a return within one or two years. The CPI and advanced materials sectors will not adopt HT methodology until commercial impacts are validated, and the R&D capital assets can be economically utilized. The bulk of the smaller firms manufacturing specialty chemicals and materials would conceivably be a target customer, however their entry will be retarded pending reduced entry costs. These industries are characterized by R&D budgets that are typically 3% to 4% of sales, with profit margins in the range of 8% to10%.[1] As indicated earlier, improved return on RD&E investment and faster time-to-product launch are expected to result in higher overall NPV. Because the CPI and materials sectors generally exhibit cycle times of 7 to10 years for concept-to-product launch, given end-user qualification and manufacturing design and construction cycles, HT RD&E projects initiated now will not reach commercial validation until 2003-2005 at the earliest.

Notably, numerous large companies have reported publicly that their HT RD&E efforts *have* been technically successful in catalyst discovery and process development, at a typical entry cost of $5M to $20M.[21] In order to reach a competitive critical mass, HT RD&E methodologies must reach industries and companies that cannot make such a substantial capital investment. There is, therefore, a role for the Federal Government to gain a significant impact on the national economy by investing in the development of new, lower-cost tools that will ultimately reduce entry costs for industries that find implementation prohibited.

VI. ANALYSIS OF SOLUTION

The implementation of this emerging *methodology* by the advanced materials industry will enable new *technologies* having broad technological and economic impact. The principal drivers are lower development costs, reduced innovation cycle times, and higher performance materials for industrial and consumer products--to impact the accelerating market needs of "faster-less expensive-better".

Since February 1998, the NIST ATP has been collecting input on the needs of U.S industry for new techniques and strategies for HT R&D. The role of government support in response to industry needs in a relevant time frame, and the economic value to taxpayers of a potential investment, are important considerations.

VII. COMMERCIAL OBJECTIVES

A. BACKGROUND

A new paradigm is now taking hold in the RD&E centers of Japanese, European, and U.S. advanced materials industries of catalysts, polymers, specialty and fine chemicals, optical materials, and electronic materials.[22] High throughput methods[2] for materials RD&E leverages the combinatorial chemistry methodologies developed over the past ten years in the pharmaceutical industry. The implementation of this emerging *methodology* by materials innovators will enable new *technologies* having broad technological and economic impact as manufacturers strive to meet original equipment manufacturer (OEM) demands. The bottom line is that more complex compositions can be created and analyzed in a reduced cycle time and at lower cost. The flip side is that this should also be a watershed for basic research in elucidating new phenomena as well as in developing the new technology platforms.

Since February 1998, the NIST ATP has been gathering primary and secondary market research through an Industry Working Group, by holding public workshops (3 March1998, 28 Nov1998, 16Nov1999), and by a proactive outreach effort at conferences and workshops. The NIST ATP leveraged this knowledge base to understand U.S. industry needs with respect to the ATP Mission. The ATP's cost-sharing of high-risk industrial research appears to correlate uniquely to industry's critical success factors.[23]

There are significant scientific and technological challenges to implement HT methods in advanced materials. These challenges can borrow from advances made in other areas such as drug discovery and bioinformatics, however in most cases the technology transfer is not straightforward. The transfer of traditional *serial* research methodologies to *parallel* methodologies will require the integration of otherwise diverse computational and characterization tools for library design (statistics, design of experiments), library fabrication (sample deposition, automation), characterization (sensors, automation, data acquisition), and informatics (data handling, visualization, decision tools). The scalability of the results obtained will require scientific and technological advances in the areas of interfacial effects and structure-property prediction.

As OEMs and materials manufacturers focus on their core business areas--assembly and manufacture--the advanced materials industries are beginning to outsource discovery and process development. This is resulting in the formation of, and dependence on, small firms that are structured as discovery- and/or high throughput methods service providers (the "discovery and process development industry"). There are currently seven of these service firms world-wide, and their competencies lie in an ability to focus integrated hardware and software systems toward profitable research areas such as catalysts and electronic materials. The HT RD&E environment includes materials manufacturers, discovery service providers, and hardware and software tool providers (Figure 7).

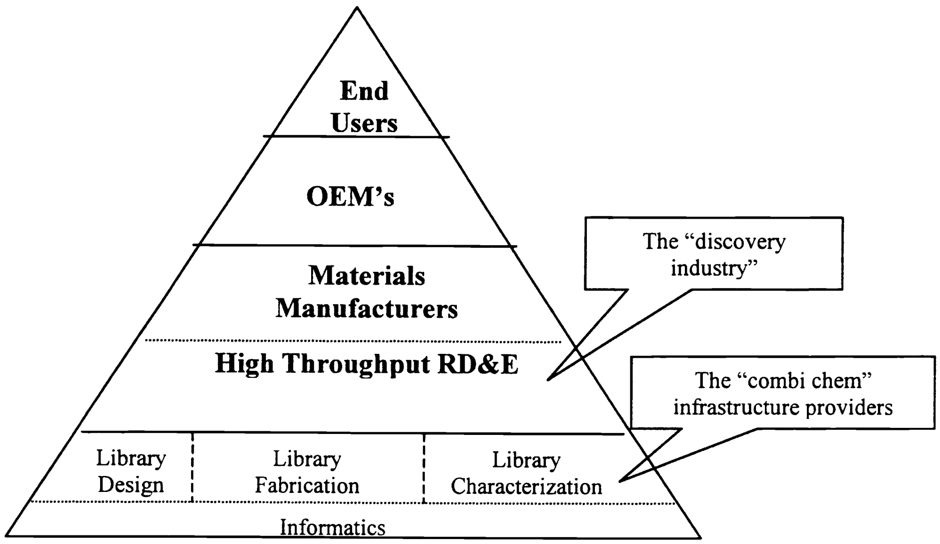

FIGURE 7. THE MATERIALS INDUSTRIES HIERARCHY

B. IMPACT ON INDUSTRY

ATP's support of industrial implementation of high throughput methods could significantly improve the competitive stance of U.S. industry and provide broad economic impact. Industry representatives have indicated that a reduction in the time to launch a new catalyst for chemicals manufacture can be reduced approximately two years utilizing HT discovery methods. This two-year reduction in break-even point (BEP) may approach $20M for a typical $100M chemical plant. ATP can further decrease the time-to- market through co-funding the high-risk development of new tools that would normally be beyond the scope of traditional industrial research, resulting in a higher Net Present Value (NPV).

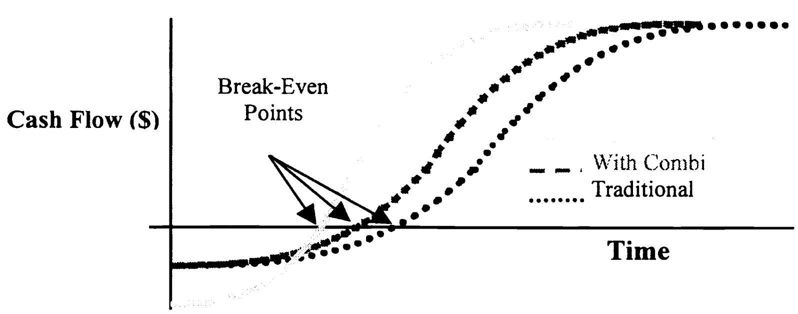

FIGURE 8. ATP FUNDING IMPACTS TIME-TO-MARKET FOR HIGH-RISK TECHNOLOGIES

One market factor that might predict the movement of HT RD&E methods is the current level of spending for R&D in these sectors. Implementation of HT RD&E 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 (OEM's), and analytical instruments and software sectors provide technology infrastructure. The annual R&D budgets for these firms are an indicator of the leverage that HT methods can have: assuming a 5% penetration into the infrastructure ($9.7B in 1997) and supplier sector R&D ($13.4B), approximately $1.2B in R&D budgets would be assigned to high throughput methods development with a potential downstream increase of $905B in sales (pharmaceuticals excluded).

High throughput methods will eventually impact all of the advanced materials industries and high technology industries, therefore the potential impact of the ATP technology cluster "Combinatorial Methods for Materials R&D" could be large. Funding for two projects awarded in the ATP FY1999 Open Competition is shown below.

Nonlinear Dynamics/UOP LLP	**"Combinatorial Tools and Advanced Data Analysis Methods for Heterogeneous Catalysts"** **$14,715K (ATP) + $15,186 (joint venture, 5 year duration)**
GE/Avery-Dennison	**"Combinatorial Methodology for Coatings Development"** **$3,127K (ATP) + $3,200K (joint venture, 3 year duration)**

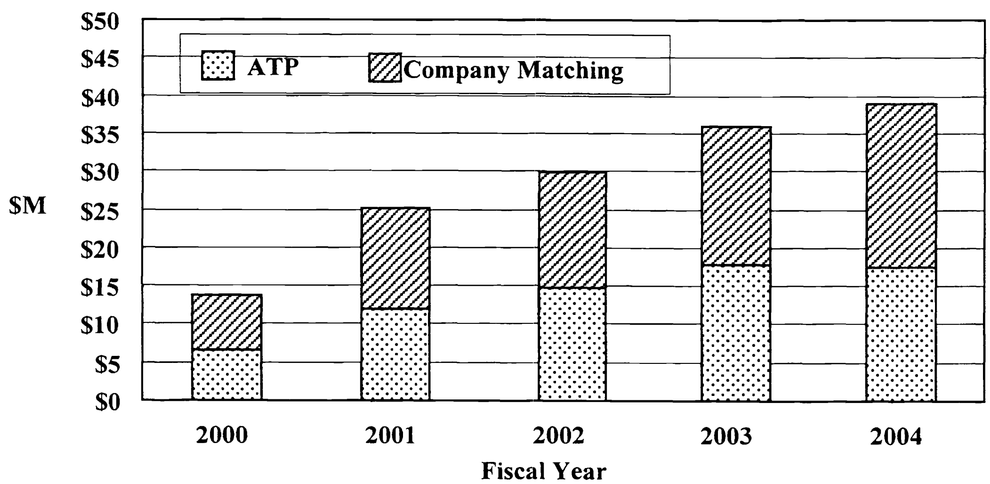

FIGURE 9. TOTAL ATP AND INDUSTRY INVESTMENT

ATP can also have an important and probably unique role in funding research at NIST in this area through Intramural Funding. This research addresses fundamental problems in developing new standards and measurement techniques that will find general use by U.S. industry. Research funded for FY2000 through the ATP Intramural program will focus on:

- developing the infrastructure to support new parallel methodologies and measurement tools that can be tailored to industrial applications and properties;
- validating new and existing methods and models for small sample sizes analyzed using high throughput approaches;
- validating the applicability of HT methods to new materials and research problems.

The NIST Measurements and Standards Laboratories (MSL) are uniquely qualified to participate in this area: NIST's broad capabilities for scientific research and technology development funding address major challenges of high throughput methods implementation. ATP is currently funding research in the areas of polymer array scaffolds for tissue engineering,[24] two-dimensional infrared array detection of inorganic and organic substrates,[25] x-ray and microwave measurement of dielectric ceramic thin films,[26] analysis of dopants in compound semiconductor thin films,[27] x-ray studies of supported catalysts,[28] and genetic programming of data query engines.[29] The NIST MSL effort is expected to grow significantly.

C. TECHNOLOGICAL CHALLENGES

Materials manufacturers are utilizing several business scenarios to obtain HT RD&E capabilities: by developing internal capabilities (e.g., General Electric Corporate R&D); by contracting with service providers having a core competency in high throughput discovery methods (e.g., Dow Chemical with Symyx Technologies); or by developing an independent consortium or alliance partnership with individual tools providers (e.g., Avantium—a Shell spin-off in partnership with the Dutch government, private investors, and three Dutch universities). These events signal a clear trend that the materials industry is beginning to dis-integrate their front-end discovery efforts to smaller external entities. There are currently seven companies known to be either performing front-end R&D or developing integrated systems for large materials manufacturers utilizing HT R&D (ref. Table 5[11]).

TABLE 5. HIGH THROUGHPUT METHODS PROVIDERS FOR ADVANCED MATERIALS

Parent Company (Miscellaneous)[12]	**Company (HT Materials R&D)**	**Financing/ Partnerships**
	Symyx Technologies (Santa Clara)	IPO-11/20/99 Hoechst AG[c], Celanese[c], Bayer AG[c], BASF[c], B.F. Goodrich[c], Dow Chemical Unilever[j/v]
ArQule Inc.	Alveus Systems (Belmont, MA)	N/A
BASF	hte GmbH (Heidelberg)	MPI-Kohlenforschung BASF, Private financing
Charybdis	Scylla (San Diego)	Private financing
SRI International	CombiCat (Menlo Park)	Internal, clients
Catalytica Advanced Technologies	Aperion (Mountain View, CA)	(Announced June 1999)
Molecular Design (UK)	Cambridge Discovery Chemistry (Cambridge, UK)	BP Chemicals (Germany) DSM (Netherlands) Engelhard
Argonaut Technologies	------	Symyx Technologies
Shell Oil	Avantium	Universities of Delft, Twente, Eindhoven; the government of The Netherlands; GSE, Inc.; other shareholders.

VIII. CONCLUSION

Combinatorial methods have revolutionized drug discovery in the pharmaceutical industry and are poised to do the same in materials science, biotechnology, chemistry, physics and other technological bases. These efforts are needed to maintain U.S. leadership in chemicals and materials R&D by providing globally competitive increases in efficiency of materials discovery and process optimization. Industry has correlated the impact of increased innovation throughput in different areas to broad economic benefits.

HT methods R&D for advanced materials is about four years old.[30] Current end users for HT RD&E are the chemical process industry (catalyst discovery and chemical process development), specialty polymers, and electronic materials (e.g., inorganic dielectric and phosphor materials discovery) industries.[31] One would expect that, as the barrier to entry is reduced by lower cost tools and validation of the methodologies, lower-valued applications,[32] for example, commodity materials, will become targeted. Key commercial and technology drivers with regard to implementation of HT RD&E methods are shown in Table 6.

TABLE 6. MAPPING TECHNICAL CHALLENGES TO ECONOMIC BENEFITS

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, semi-conductors, dielectrics • Machine tools	• Higher engine temperatures, increased service life, and reduction of downtime • Higher component densities and speeds • Machining of new alloys, increased productivity

Advances in both hardware and software will be required to implement HT RD&E methods more broadly. The basic underlying software technology must be capable defining profitable experimental spaces and visualizing complex data relationships, and of correlating 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 statistical experimental design engines on the front end while remaining compliant with enterprise-wide systems for knowledge management and maintaining control of experimental hardware.

Through competitive proposal submissions from industry teams to the ATP Open Competitions, the ATP can reduce the cost of implementing high throughput RD&E by cost-sharing the high technical-risk aspects of developing new, generic tools so that cost-sensitive industrial sectors will be able to invest in this new capability. Successful proposals to the ATP have the potential to facilitate the emergence of new technology platforms by stimulating the development of partnerships; it can spur the fusion of new technologies for subsequent diffusion to other areas; it can facilitate the integration of complex systems; it can help the integration of otherwise diverse technologies.

REFERENCES

[1] 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.

[2] *The Global Competitiveness Report*, 1996, World Economic Forum, Geneva, Switzerland WORLD BANK, *From Plan to Market: World Development Report 1996*, NSF, Science and Engineering Indicators, 1996.

[3] Jandeleit B, Schaefer DJ, Powers TS, Turner HW, Weinberg WH "Combinatorial Materials Science and Catalysis," *Angewandte Chemie-International Edition* **1999,** 38: (17) 2495-2532.

[4] Five industry White Papers have been received in this area by the ATP. In addition, pre- and full proposals were submitted to the FY1999 ATP Open Competition with two substantial awards made; significant requests have been made to the ATP Combinatorial Methods web site; ATP public Workshops held in 1998 and 1999 drew approximately 75 and 50 representatives, respectively; and continued interest is being expressed in workshops attended by ATP staff.

[5] Cawse, J., "Information Based Strategies for Combinatorial and High Throughput Materials Development: A White Paper," General Electric Co. Corporate R&D, 11/1999.

[6] Symyx Technologies, Inc., Santa Clara, CA. "Symyx's patent estate today includes eight issued U.S. patents, as well as more than 155 patent applications in the U.S. and abroad. Symyx's comprehensive intellectual property portfolio includes patents, patent applications and trade secrets directed toward composition of matter, libraries, synthesis and high throughput screening methodologies, instrumentation and software" ref. http://www.symyx.com; Patents issued: U.S. Patent 6,030,917, U.S. Patent 6,004,617 and U.S. Patent 5,985,356.

[7] Koinuma H., Koida T, Ohnishi T, *et al.* "Parallel fabrication of artificially designed superlattices by combinatorial laser MBE," *Appl. Phys. A-Mater.* **1999**, 69: S29-S31; Matsumoto Y, Murakami M, Jin ZW, *et al.*, "Combinatorial laser molecular beam epitaxy (MBE) growth of Mg-Zn-O alloy for band gap engineering," *Japan. J. Appl. Phys.* **1999**, 2 38: (6AB) L603-L605.

[8] For-profit organizations (Knowledge Foundation, CHI, The Catalyst Group, etc.) as well as non-profit organizations (American Chemical Society, American Physical Society, Materials Research Society, Association of Industrial Chemical Engineers, etc.) have held extensive public discussions of this area. Consultation of the corresponding web sites will re-direct interested parties to specific events. In addition, the ATP has held three public workshops: http://www.atp.nist.gov/www/ccmr/ccmr_off.htm.

[9] Symyx Technologies press release, April 7, 1999 and Prospectus filed with the U.S. Securities and Exchange Commission on November 17, 1999 prior to their Initial Public Offering (http://www.sec.gov).

[10] http://www.wavefunction.com

[11] http://www.msi.com

[12] Ref. K.F. Jensen *et al.* Massachusetts Institute of Technology; R.S. Wegeng *et al.* Pacific Northwest National Laboratories; W. Ehrhard *et al.* Instut für Mikroteknik Mainz; J.F. Ryley *et al.* DuPont, etc.

[13] Catalytic micro-reactor with integrated heaters, temperature and flow sensors. Reactants enter at the ends of the bar of the T-shaped reactor, mix and react in the heated channel over a catalyst, and exit at the end of the channel. Ref. Gleason *et al.*, http://web.mit.edu/cheme/www/People/Faculty.

[14] W. Ehrfeld, IMM, Mainz, Germany.

[15] http://www.fzk.de/pmt/

[16] R.S. Wegeng, PNNL, Redland, WA.

[17] K.F. Jensen, MIT, Cambridge, MA, http://www-mtl.mit.edu/mtlhome/.

[18] D.L. Quiram *et al. Proceedings of the 2000 AIChE Spring Meeting, 4th International Conference on Microreaction Technology*, 06 March 2000.

[19] DARPA MicroFLUMES Program, http://www.darpa.mil/MTO/mFlumes/index.html.

[20] D.A. Hicks, "Time Wars: Is There a Financial Undertow from Accelerating Technical Advance?" *R-T Management* **2000**, p. 34-39.

[21] For example, trade journals and presentations at recent public meetings include statements by UOP LLC, General Electric, DuPont, Dow Chemical, BASF, Shell, etc.

[22] Fairley P., *Chemical Week*, August 11, 1999, pp. 27-33, and references therein.

[23] Ref. SWOT Analysis of U.S. industry *vis á vis* combinatorial methods, Appendix Figure 6 http://www.atp.nist.gov/www/ccmr/public.pdf.

[24] Amis E. *et al.* Polymers Division, Materials Science and Engineering Laboratory, NIST.

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[27] Handwerker C. *et al.* Metallurgy Division, Materials Science and Engineering Laboratory, NIST.

[28] Fischer D., Ceramics Division, Materials Science and Engineering Laboratory, NIST.

[29] J. Devaney and J. Hagadorn, High Performance Computing Division, Information Technology Laboratory, NIST.

[30] Xiang XD, Sun XD, Briceno G, Lou YL, Wang KA, Chang HY, Wallacefreedman WG, Chen SW, Schultz PG, "A Combinatorial Approach To Materials Discovery," *Science* **1995,** , 268: (5218) 1738-1740.

[31] Current age depends on what is considered combinatorial chemistry. M. Geisen, the "father of combinatorial chemistry" published his first research paper in the 1980's, and Merrifield's Resin has long been used for separations, but the methods did not become accepted and automated until the early 1990's. Ref. *J. Combinatorial Chemistry* **1999**, *1(1)*, 3-10.

[32] Combinatorial methods are most suitable to compositionally-driven materials previously discovered (laboriously) using purely empirical methods and serial methodologies.