HIGH THROUGHPUT METHODS* FOR MATERIALS RESEARCH:

A GROWING EFFORT AT NIST

John D. Hewes, Ph.D.
Program Manager
Advanced Technology Program
National Institute of Standards and Technology
Gaithersburg, MD 20899-4730 USA

email: john.hewes@nist.gov
http://www.atp.nist.gov/www/ccmr/ccmr_off.htm

*aka "Combinatorial Chemistry"

Agenda

- NIST's Mission and role in High Throughput Experimentation (HTE) methods
- ATP portfolio in HTE/combinatorial methods
- NIST MSL efforts in HTE
- Key drivers: productivity and profitability
- Vision 2020 Road Map of Research Needs
- Conclusion

NIST Assets Include:

Advanced Technology Program (ATP)

Partnership with private industry to accelerate the development of high-risk, enabling technologies with broad benefits for the entire economy and for society.

Measurements and Standards Laboratories (MSL)

Nation's ultimate reference point for measurements, standards, and technology research to support industry, science, health, safety, and the environment.

Manufacturing Extension Partnership

Network of centers offering technical assistance and best business practices to the 385,000 smaller manufacturers in all 50 states and Puerto Rico.

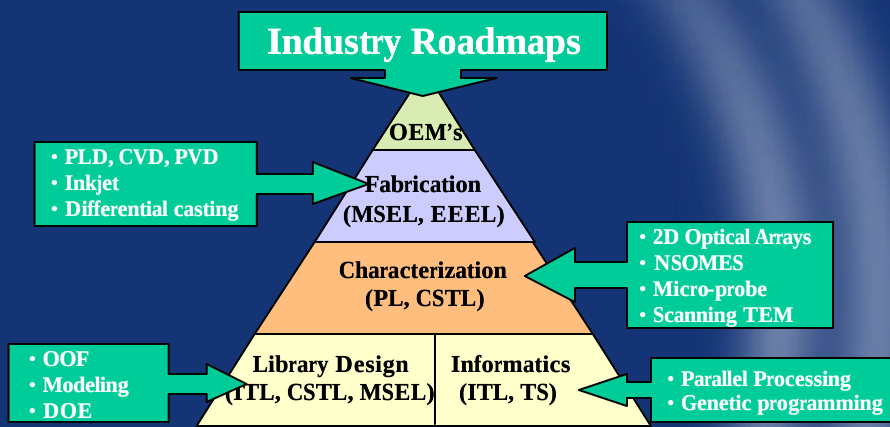
Baldrigde National Quality Program

Promotes business performance excellence and quality achievement by U.S. companies.

HTE at NIST

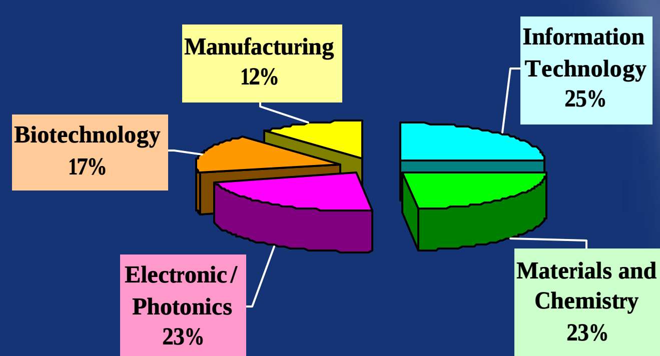
- **Support new parallel methodologies and measurement tools tailored to specific industrial applications and properties;**
- **Validate new and existing measurement methods and models for small sample sizes analyzed using parallel or high throughput approaches;**
- **Supply comprehensive standard reference materials libraries and data (faster and / or better);**
- **Demonstrate application of HTE / combinatorial methods to new materials and R&D problems.**

The NIST MSL Opportunity



Industry/University/NIST Consortia are Being Built
Contact: combi@nist.gov

522 ATP Awards Since 1990



By Technology Area,
Percent of $1,640 M Awarded

ATP Investment Portfolio in HTE

Nonlinear Dynamics/UOP LLP $14,715K (ATP) + $15,186 (5 yrs.)
"Combinatorial Tools & Advanced Data Analysis Methods for Heterogeneous Catalysts"
Develop novel combinatorial methods for the discovery of new, more effective heterogeneous catalysts used by the chemical industry, thereby increasing the efficiency of catalyst research and development.

GE/Avery Dennison $3,127K (ATP) + $3,200K (3 yrs.)
"Combinatorial Methodology for Coatings Development"
Develop combinatorial methods to achieve several orders of magnitude increase in the rate of screening of new coatings for the automotive and information display industries, accelerating the introduction of new products while also improving their quality.

ChemCodes, Inc. $2,000K (ATP) + $2,603K (2 yrs.)
"Experimental Generation of the First Complete Chemical Reaction Database"
Use high-throughput reaction screening coupled with quantitative mass spectrometry to create the first comprehensive, experimentally derived chemical reactivity database for organic molecules, leading to novel and efficient pathways for synthesizing new compounds.

Albemarle Corporation $1,989K (ATP) + $2,143K (3 yrs.)
"Single-Site Catalysis: The Next Frontier"
Develop new families of well-characterized, highly efficient catalytic activators for use with metallocenes and other single-site catalysts to reduce costs and enable better product control in the production of polyolefin plastics.

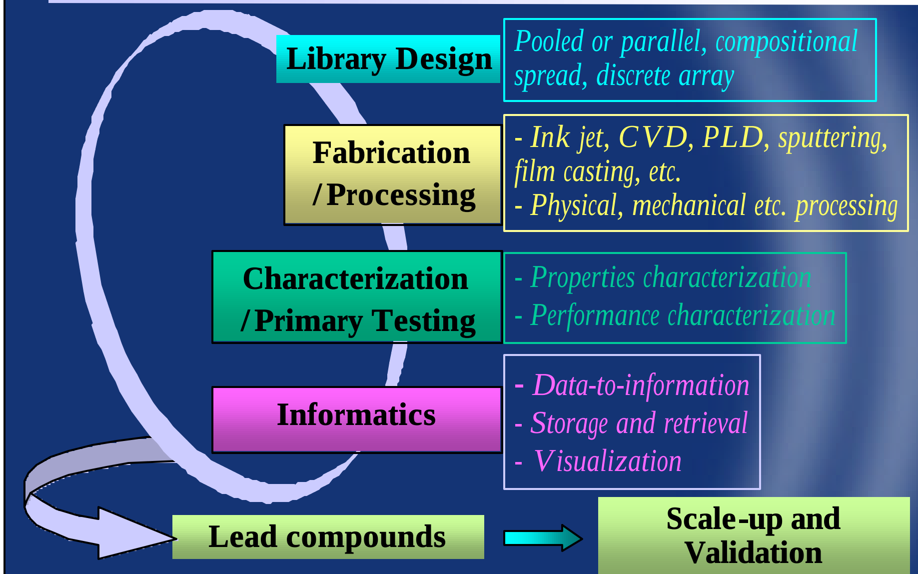
ATP Intramural Support at NIST

Lab	ATP Intramural Funding: Technical Area
MSEL-Ceramics	NEXAFS: Scanning X-Ray Studies of Supported Catalysts
CSTL	Micro-hotplates and micro-sensors
MSEL-Polymers	Polymer Scaffolds for Engineered Tissue
ITL	Genetic programming for Data Visualization and Mining
CSTL/MSEL/ITL	Microwave microscopy of BST Thin Layer Dielectrics
Physics Lab	2-D FTIR. imaging

CSTL - Chemical Sciences and Technology Lab
MSEL - Materials Science and Technology Lab
ITL- Information Technologies Lab

Continuing FY2001 Ended FY2000

High-throughput Experimentation



HTE improves innovation processes

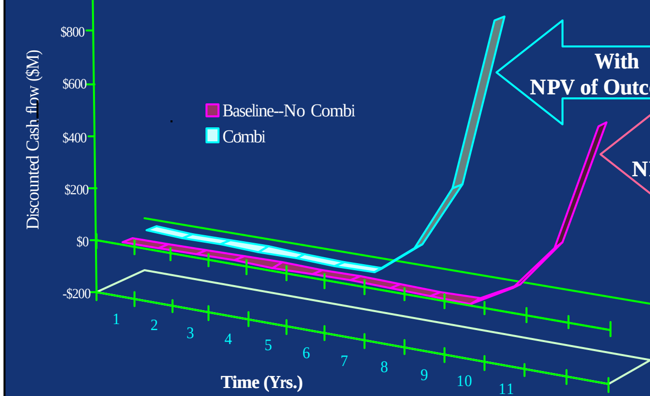
- **Reduced innovation cycle times across organization**
  - *Implementation in discovery phase can save two years off of usual 10-year commercialization cycle*
  - *Implementation in process and product development*
  - *Implementation in customer service and (flexible) manufacturing*
- **More efficient use of R&D and manufacturing**
  - *ROI of R&D $'s*
  - *Decreased labor cost per experiment using using automation (>100-fold)*
- **Enables discovery in huge experimental spaces**
  - *Probability of success in discovery phase increases from 20-30% to >50%*
  - *Broadens spectrum of materials in development*

The Value of HTE in Discovery Phase

Pro Forma[1] example:

Pharmaceutical Chemicals Discovery[2]

Loaded R&D Costs/Compound = $19 vs. $9,000



With HTE
NPV of Outcome: $286 M

Without HTE
NPV of Outcome: $203 M

ASSUMPTIONS: Company Implements Combi discovery	
Total BR time	0.3
No. chemists needed	4
No. compds Tested	~9,000
No. of Serial rounds	1
No. compds/Round	~9,000
Cost of screen/round	$10,000
Total costs-chemists	$167,000
Cost/Comp'd	$19

ASSUMPTIONS: Pharmaceutical Industry w/out Combi Discovery	
Total BR time	5 years
No. chemists needed	15
No. comp'ds Tested	3,750
No. of Serial rounds	250
No. comp'ds/Round	38
Cost of screen/round	$10,000
Total costs-chemists	$18.75M
Total cost/Comp'd	$5,000

1. F.P. Boer, *The Valuation of Technology: Business and financial Issues in R&D*, New York: John Wiley and Sons, Inc., 1999.
2.

Economic Benefits

Broad-based economic benefits are expected from materials and process discovery using HTE methods:

- **Downstream impacts of new materials**
- **Diffusion to other industries**
- **Diffusion to other processes**

SYSTEMS & COMPONENTS $400B

Sales* ($M)	
COMMODITY POLYMERS	$
SPECIALTY POLYMERS	$ 29,415
OPTOELECTRONICS	$ 14,000
ELECTRONIC CHEMICALS	$ 3,471
ELECTRONIC POLYMERS	$
SEPARATIONS	$ 500?

CATALYST R&D $3,585M

* Est.year 2001

A Developing Service Industry

Parent	Daughter	J/V Partners, Clients
(A. Zafaroni)	Symyx Technologies	Hoechst AG, Celanese AG, Bayer AG, BASF, Unilever, etc. IPO-11/19/99
ArQule Inc.	Alveus Technologies	N/A
MPI-Kohlenforschung BASF (silent partner)	hte GmbH hte North America	MPI-Kohlenforschung BASF (client) Molecular Simulations Inc.
Charybdis	Scylla	(single clients)
SRI International	SRI International	(single clients)
Catalytica Advanced Tech.	Catalytica NovoTec	
Shell International Chemicals (NL)	Avantium Technologies NV Avantium Technologies Inc.	Universities of Delft, Twente, Eindhoven; The Netherlands; GSE Technologies, Inc.; SmithKline Beecham/S.R. One; Alpinvest; The Generics Group, W.R. Grace, etc.

Market opportunity in catalysts is $ M alone

RD&E Early Adopters

Chemical Companies Utilizing HTE Methods

Air Liquide
Air Products
Akzo Nobel
Albemarle
Alcoa
Arch Chemicals
BASF
BP Amoco
Cabot
Celanese
Ciba Specialty Chemicals
Clariant
Cytec Industries
DSM
Dow Chemical
DuPont
Eastman Chemical
ElfAtoFina
Engelhard
Geon
Lucent Technologies
Rohm and Haas
Shell Oil
W.R. Grace

Vision 2020: Preliminary Conclusions

Library Design

Vision

- Close integration between experimentation and modeling
- Economic and business models will be used for decision making
- Most experiments done “virtually”
- Ability to solve a chemical field

Research Needs

- Integration of equipment and theory
- Models that span multiple scales: interface between micro-meso-macro scales
- Paradigm shift in experiment design
  - *Ability to process multiple experiments and results*
  - *Make the first experiment right (but integrate results from failures)*
  - *Pharmacology example*

Vision 2020: Preliminary Conclusions

Library Fabrication

Vision

- Libraries are achievable-a standard footprint is available
- Informatics/design/production are linked and web-accessible
- Virtual libraries have the ability to accurately predict
- Libraries that explore both compositional and process variables
- Vendors supply standardized equipment, universal standards for processing and calibration

Research Needs

- Sample Handling
  - *Technology for precise handling and mixing of powders and viscous liquids over high temperature, pH, pressure ranges*
- Scalability
  - *Lab scale to pilot scale predictability*
  - *Between thin films and bulk properties*

Vision 2020: Preliminary Conclusions

Library Characterization

Vision

- Correlation of performance and properties
- Scalability: micro measurements to performance levels

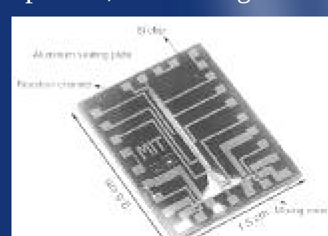
Research Needs

- Size/Scale Issues
  - *Small samples don't necessarily tell you how the whole will perform*
- Integration from sample to end-use
  - *Integrate analytical equipment with reactors, esp. microfluidic reactors coupled to detectors*
- Mechanical Properties Analysis
  - *Develop tool to measure stress-strain curves, tensile testing for 100 micro-samples*
- Structure
  - *Structural characterization—robust, sensitive, accurate, fast (x-ray system)*

Fabrication and Characterization

Key Issues— Micro-Reactor Technology

- Understanding and exploiting surface effects (CFD/modeling)
- Integration of reactors, sensors, controllers on-chip
- Chip substrates: reactivity, thermal properties, machining
- Fluidic and electronic interconnects
- Mixing, separations, heat transfer
- Sample deposition
- Scalability Predictions
  - *Interfacial properties*
- Process control
  - *Temperature/pressure at much higher throughput*



Ref. Gleason *et al., http://web.mit.edu/cheme/www/People/Faculty.*

Vision 2020: Preliminary Conclusions

Informatics

Vision

- Open collaboration through standard data structures
- Platform independence, central data storage
- Decision-making and knowledge infrastructure for R&D
- Researchers will move to probability-based approaches

Research needs

- Develop expanded data visualization tools
- Develop standard interface for instrumentation in general
- Robustness and quality (six sigma)
- Develop alternative to current relational database technology
  - *Dynamically updateable architectures-database design, implementation, modifications*

Informatics

Key Issues--Advanced Data Handling

- High-performance data mining tools to extend utility of a database management system;
- Atomic level to engineering design by developing relationships:
  - Properties = f (chemistry, processing, microstructure…)
- Integration of diverse databases for functionally specific data bases;
- Quantitative Structure Property Relationships (QSPR);
- Development of a query language that links different methods for querying the data.

ATP Plan Forward—FY ‘01

Challenges for High Throughput RD&E

Computational

- **Library Design**
  - Computational/Modeling: QSPR
  - Statistics and control of error
  - Design of Experiments
- **Informatics**
  - Increasing Information/Bandwidth
  - Experimental complexity
  - Data integration/analysis
  - Hardware control / interfacing
  - Expert systems for data analysis

Micro-Reactor Technologies

- **MEMS**
  - Lab-on-chip
  - Embedded sensors
  - Mechanical sensors
- **Automation**
  - 10^2 -10^3 throughput increase
  - Reproducibility
- **Economies of scale**

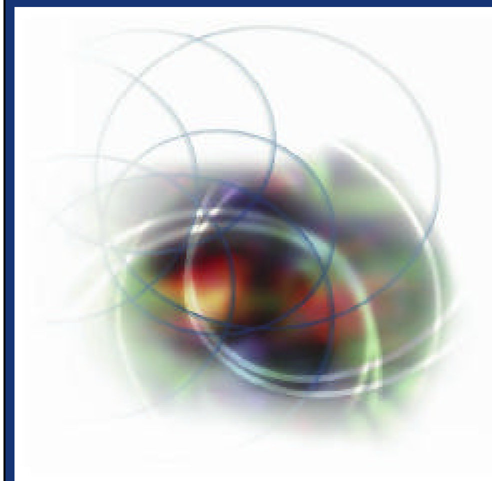
Conclusions

Chemical and Materials Industries Feedback:
Step-change innovations in R&D methods are needed to maintain competitive positions.

Key enabling technology areas are:

- **Information technologies (informatics)**
  - *Problem*: Bottleneck in data-to-knowledge process
  - *Solution*: Leverage the convergence of inexpensive computational engines and distributed data warehouses
- **Micro-reactor technologies**
  - *Problem*: “Mass production” drives economics for high throughput screening
  - *Solution:* MEMS-based reactors as R&D factories provide higher densities.

ATP National Meeting



Funding Opportunities for High-Risk Research

June 4-6, 2001

Wyndham Baltimore Inner Harbor Hotel
101 West Fayette Street
Baltimore, Maryland

Check for Regional Meetings
www.atp.nist.gov
1-800-ATP-FUND

Contact Information

John D. Hewes, Ph.D.

Advanced Technology Program
National Institute of Standards and Technology
100 Bureau Dr., Stop 4730
Gaithersburg, MD 20899-4730
Tel. (301) 975-5416
FAX: (301) 548-1087
email: john.hewes@nist.gov

http://www.atp.nist.gov/www/ccmr/ccmr_off.htm