Keynote Address:

Economic Impact of Combinatorial Chemistry on Industry and Society

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Agenda

- NIST’s Mission and role in HTE methods
- The Advanced Technology Program
- ATP funding in HTE/ combinatorial methods
- Increased productivity and profitability
- Vision 2020 Road Map of Research Needs
- Conclusion
NIST Assets Include:

**Advanced Technology Program**
- 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**
- 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.

**Baldrige National Quality Program**
- Promotes business performance excellence and quality achievement by U.S. companies.

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**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 Competencies

- OEM’s, e.g. industry roadmaps
- Fabrication (MSEL, EEL)
- Characterization (PL, CSTL)
- Library Design (ITL, CSTL)
- Informatics (ITL, TS)

- MSL
- • PLD, CVD, PVD
- • Inkjet
- • Differential casting
- • 2D Optical Arrays
- • NSOMES
- • Micro-probe
- • Scanning TEM
- • Parallel Processing
- • Genetic Programming

Contact: combi@nist.gov

522 ATP Awards Since 1990

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

- Manufacturing 12%
- Biotechnology 17%
- Electronic/Photonics 23%
- Information Technology 25%
- Materials and Chemistry 23%
**ATP Technology Cluster**

**Nonlinear Dynamics/UOP LLP**

“Combinatorial Tools and 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**

“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.**

“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**

“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.

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**ATP Intramural Support at NIST**

<table>
<thead>
<tr>
<th>Lab</th>
<th>ATP Intramural Funding: Technical Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSEL-Ceramics</td>
<td>NEXAFS, Scanning X-Ray Studies of Supported Catalysts</td>
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<tr>
<td>CSTL</td>
<td>Micro-hotplates and micro-sensors</td>
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<tr>
<td>MSEL-Polymers</td>
<td>Polymer Scaffolds for Engineered Tissue</td>
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<tr>
<td>ITL</td>
<td>Genetic programming for Data Visualization and Mining</td>
</tr>
<tr>
<td>CSTL/MSEL/ITL</td>
<td>Microwave microscopy of BST Thin Layer Dielectrics</td>
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<tr>
<td>Physics Lab</td>
<td>2-D FTIR imaging</td>
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CSTL - Chemical Sciences and Technology Lab
MSEL - Materials Science and Technology Lab
ITL - Information Technologies Lab

Continuing FY2001  Ended FY2000
High-throughput Experimentation

**Library Design**
- Pooled or parallel, compositional spread, discrete array

**Fabrication / Processing**
- Ink jet, CVD, PLD, sputtering, film casting, etc
- Physical, mechanical etc processing

**Characterization / Primary Testing**
- Properties characterization
- Performance characterization

**Informatics**
- Data-to-information
- Storage and retrieval
- Visualization

**Lead compounds**

**Scale-up and Validation**

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**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 in chemical industry
  - Implementation in process and product development (emerging)
  - Implementation in customer service and (flexible) manufacturing (vision)

- **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%
  - Broaders spectrum of materials in development
The Value of HTE in Discovery

Pro Forma example
Basis Pharmaceutical / Chemical Company

With HTE NPV of Outcome: $286 M
Without HTE NPV of Outcome: $203 M

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

U.S. Sales* ($M)
- BASIC CHEMICALS $115,576
- SPECIALTY POLYMERS $29,415
- OPTOELECTRONICS $14,000
- SPECIALTY CHEMICALS $50,124

CATALYST R&D $3,585M
A Developing Service Industry

<table>
<thead>
<tr>
<th>Parent</th>
<th>Daughter</th>
<th>J/V Partners, Clients</th>
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<tbody>
<tr>
<td>(A. Zafaroni)</td>
<td>Symyx Technologies</td>
<td>Hoechst AG, Celanese AG, Bayer AG, BASF, Unilever, etc.</td>
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<tr>
<td>ArQule Inc.</td>
<td>Avesus Technologies</td>
<td>N/A</td>
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<tr>
<td>MPI-Kohlenforschung BASF</td>
<td>hte GmbH</td>
<td>(MPI-Kohlenforschung BASF (silent partner)</td>
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<td></td>
<td>hte North America</td>
<td>BASF (client)</td>
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<td></td>
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<td>Molecular Simulations Inc.</td>
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<td>Charybdis</td>
<td>Scylla</td>
<td>(single clients)</td>
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<td>SRI International</td>
<td>SRI International</td>
<td>(single clients)</td>
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<td>Catalytica Advanced Tech.</td>
<td>Catalytica NovoTec</td>
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**Market opportunity in catalysts is $300-500M**

RD&E Early Adopters
Chemical Companies Utilizing HTE Methods

- Air Liquide
- Air Products
- Akzo Nobel
- Albemarle
- Alcoa
- Arch Chemicals
- Avery Dennison
- BASF
- BP
- Cabot
- Celanese
- Ciba Specialty Chemicals
- Clariant
- Cytec Industries
- DSM
- Dow Chemical
- DuPont
- Eastman Chemical
- ElfAtoFina
- Engelhard
- Geon
- General Electric
- Lucent Technologies
- Rohm and Haas
- Shell Oil
- UOP
- W.R. Grace
Vision 2020 Road Map

- **Technology Vision 2020** is a call to action, a strategic plan, for the U.S. chemical industry
  - CCR, ACS, AIChE, SOCMA, ACC
  - New Chemical Science and Engineering Technology (CCR)

- June 2, 2000 at NIST re: combi methods for materials
  - Approx. 40 participants from industry, government, academia
  - Vision and research needs out to the year 2020
  - Final report due March, 2001

Key Research Needs Identified

**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**
Key Issues—Fabrication and Characterization

**Micro-Reactor Technology**
Integration of reactors, sensors, controllers on-chip

- Understanding and exploiting surface effects (CFD / modeling)
- 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.

Key Issues--Informatics

**Advanced Data Handling**

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

Step-change processes are noted by industry as necessary in the following:

- Information technologies
  - Chem- and Bio-informatics leverage the convergence of inexpensive computational engines and distributed data warehouses

- Micro-reactor technologies
  - MEMS-based reactors for both distributed manufacturing systems and in R&D settings provide higher densities and mass production drive economies of scale for high throughput screening

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

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Vision 2020

BACK-UP SLIDES
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

**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
  - Microfluidic reactors coupled to detectors
- Mechanical Properties
  - Develop tool to measure stress-strain curves, tensile testing for 100 microsamples
- Structure
  - Structural characterization—robust, sensitive, accurate, fast (x-ray system)
- Tools (general)
  - Catalyst performance measurements
  - Low cost tools to measure gloss, hardness, etc.

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
- Modular tool kit—infrastructure for many different applications
- Develop standard interface for instrumentation in general
- Robustness and quality (six sigma)
- Develop alternative to current relational database technology
  - Reducing work in database design, implementation, modifications
  - Dynamically updatable architectures
- Tools to integrate and analyze structured and unstructured data
Project Selection Criteria

- **Scientific and Technological Merit (50%)**
  - Innovation in technology
  - High technical risk and feasibility
  - Quality of R&D plan

- **Potential for Broad-Based Economic Benefits (50%)**
  - Economic benefits
  - Need for ATP funding
  - Pathway to Economic Benefit

Changes to the Proposal Submission Process

- Streamlined proposal process (STAGE-GATE)
- Continual acceptance of proposals (Jan. 10th start date)
- Project selection criteria and review remain the same
- Electronic submissions of proposals (2002?)
- Regional workshops will include how to apply and opportunity to meet ATP staff for 1:1 discussions
  - Las Vegas-Alexis Park: February 1, 2001
  - NIST-Gaithersburg: February 6, 2001

check our website (www.atp.nist.gov/regionalmeeting)
Common Proposal Weaknesses: Technical

- **Lack of sufficient detail**
  - How you will reach technical objectives
  - What’s innovative (“What is the technological nugget?”)
  - Why a risky technical approach is needed
- **Unsupported assertions**
- **Outside ATP mission**
  - Low risk - product development
  - Lacks demonstrated feasibility - basic research
  - Scale up or demo to only prove economics
- **Lacks connection between technical goals & business opportunity**

Common Proposal Weaknesses: Business

- **Lacks connection between technical goals and business opportunity**
  - Competitive analysis is lacking
- **Poorly developed (or no) commercialization plan that does not incorporate business partners, distribution channels, business development/marketing/sales personnel, manufacturing, OR CUSTOMERS (!)**
  - Include MOU’s/LOA’s/etc only if favorable to proposal
- **Business plan too innovative!**
- **Insufficient evidence of economic benefits**
  - How will technology benefit company and also benefit U.S. economy
  - BE AS QUANTITATIVE AS POSSIBLE!
Outside ATP mission

- "Low risk - product development"
- "Lacks demonstrated feasibility - basic research"
- "Edisonian - we don't fund boundary-less projects"
- "What's so innovative about systems integration?"
- "Why is this risky? ... it's just software and hardware engineering best practices"
- Insufficient evidence of broad economic benefits

Doesn't paint the big picture early on

- You need to communicate a multi-disciplinary project to specialists

HAVE AN INDEPENDENT PARTY READ PROPOSAL!