Decision Support Systems for the Practicing Medicinal Chemist

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Summary of Talk

- Some history
- Some philosophy
- Some current progress

Some history

Situation in 1970

- P. Gund at American Cyanamid Agric. Res. Center, Princeton NJ - Bench Chemist, Animal Health Discovery
  - Beginnings of computer support - GE Timesharing, QSAR apps.
- Guenter Grethe, Hoffman-LaRoche, Nutley NJ - Project Leader, Drug Discovery
- NIH Biomolecular Research Resource, Princeton University
  - W. Todd Wipke, Computer aided synthesis
  - Robert Langridge, protein and nucleic acids modeling
  - P. Gund joined - 3-D Modeling of molecules; pharmacophores
  - G. Grethe sabbatical - computer representation of reactions

Some history

Situation in 1973

- Peter Gund to Merck Labs, Guenter back at Roche
- Mainframe systems for chemical information handling, biological data handling
  - Chemical Typewriter representation of chemical structures
  - Chemical information specialists to enter, search, report data
- Chemists used “punch cards”, index cards to organize project data
- Alerting publications/services to assess literature
- Only theoreticians did modeling and simulation studies
- Breakthrough - graphical, “user-friendly” interface

Some history

Molecular Modeling at Merck

- **Started as hands-on system for chemists to use (1973)**
  - Several successful applications: *Science* 208, 1425 (1980)
  - Over 100 chemists using the Merck Modeling System by 1983
- **Obtained macromolecular modeling system (1981)**
  - Protein crystallography group founded at same time
  - Hired specialized applications staff to use this equipment
  - Soon grew to 10 applications modelers at 2 sites
  - As no. of specialists ↑, no. of chemists using systems slowly ↓
- **Trended to specialized systems and hardware for experts**
  - Networked SGI graphics terminals
  - Mix of in-house and commercial software (Polygen)
  - Supercomputers (IBM, then Cray)

Some history
Merck chemists' use of other applications

- Chemists got desktop terminals, then Macs and PCs
- Terminal-accessed applications
  - Merck Modeling System, RS/1, MACCS, REACCS, e-mail, ...
- Then desktop applications
  - Filemaker, ChemDraw, MSOffice, ISIS/Base, ...
  - Terminal emulation on PCs to access earlier applications
- Then client-server applications: ISIS, ISIS/Host to Oracle, ...
- Then Web applications: internet/intranet
- Ever more applications!
  - Data handling, structure handling, literature searching
  - Spectra, robots, sequence info, ...
  - Again: 3D molecules...

Some history

Medicinal Chemists' Role at Pharmacopeia

- **High-throughput screening of combinatorial libraries**
  - 7 million compounds, hundred-millions of datapoints
  - Pharmacopeia Information Environment (PIE)
- **Design and synthesis of combinatorial libraries**
  - Library enumeration, properties prediction, selection
  - LibDraw, LibProp, Cerius2/Combichem, C2/Diversity
- **Optimization of Lead Compounds**
  - Pharmacophore-based design, structure-based design, QSAR
  - Accord for Excel, MedChem Explorer, DIVA, ...

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Some history

MDL and Modeling

- Founders (Stu Marson, Todd Wipke - 1978), other early employees were interested in molecular modeling
  - Detour into cheminformatics systems via FMC opportunity
- Early distributor of ChemLab software (Hopfinger)
- Guenter Grethe joined MDL as Senior Scientist
  - Focused on Chemical Reaction Databases
- MACCS-3D Initiative; pharmacophore search
- MDL has always had scientists interested in 3D structures
  - Doug Henry, Jim Dill, Osman Guner, Maurizio Bronzetti, Steve Muskal, Rudy Potenzone, ...
- More recently: ChemScape Chime Viewer, Sculpt, ...

Some history

Interfacing of Modeling and Informatics

- **Molecular modeling was:**
  - Calculation of preferred conformations, energetics, “fitting” to receptor site - quantitative
- **Molecular modeling is becoming:**
  - Calculation of 100’s or 1000’s of structures, properties, “docking” - semiquantitative
  - Searching of multiconformation databases for pharmacophores or shapes
- **Commercial modeling software for experts and for chemists**
  - Tripos, Accelrys, CCG, Cambridgesoft, Fujitsu, ...

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Some philosophy

What does a bench chemist do?

- Understands the goals of the project
- Understands the project background - internal, external
- Understands role on project team
- Decides what experiments to run and how
- Performs the experiments, or induce colleagues to do so
- Interprets the results
- Reports the results
- Decides what to do next

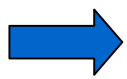
Some philosophy

What does a group leader do?

- Understands project goals, background
- Develops strategy for attacking problem
- “Sells” proposed project to management
- Assembles project team, other needed resources
- Negotiates who runs what experiments, follow up
- Collects results, interprets results, reports results
- Modifies project direction based on results, feedback
- Decides when to increase/decrease resources, modify project goals, end project, start new project

Some philosophy

How is medicinal chemistry changing?

- More targets, more throughput, more robotics
- More interdisciplinary team members
  - More non-chemical information to process/understand
- Higher throughput  faster project movement
- More expensive project decisions
- Role of computer is changing

Some philosophy

Now medicinal chemistry requires computers

- Robotic compound/library synthesis (cheminformatics)
- HTS, uHTS (discovery informatics)
- Protein crystallography, protein nmr, spectroscopy, …
- Molecular modeling/simulation utilizing structural data
- Property calculations
  - Drug-like character, ADME, Toxicity properties, SAR, …
- Data visualization to make sense of all the data
- Reaction and structure databases, but not synthesis planning tools, usually not in-house reaction databases...

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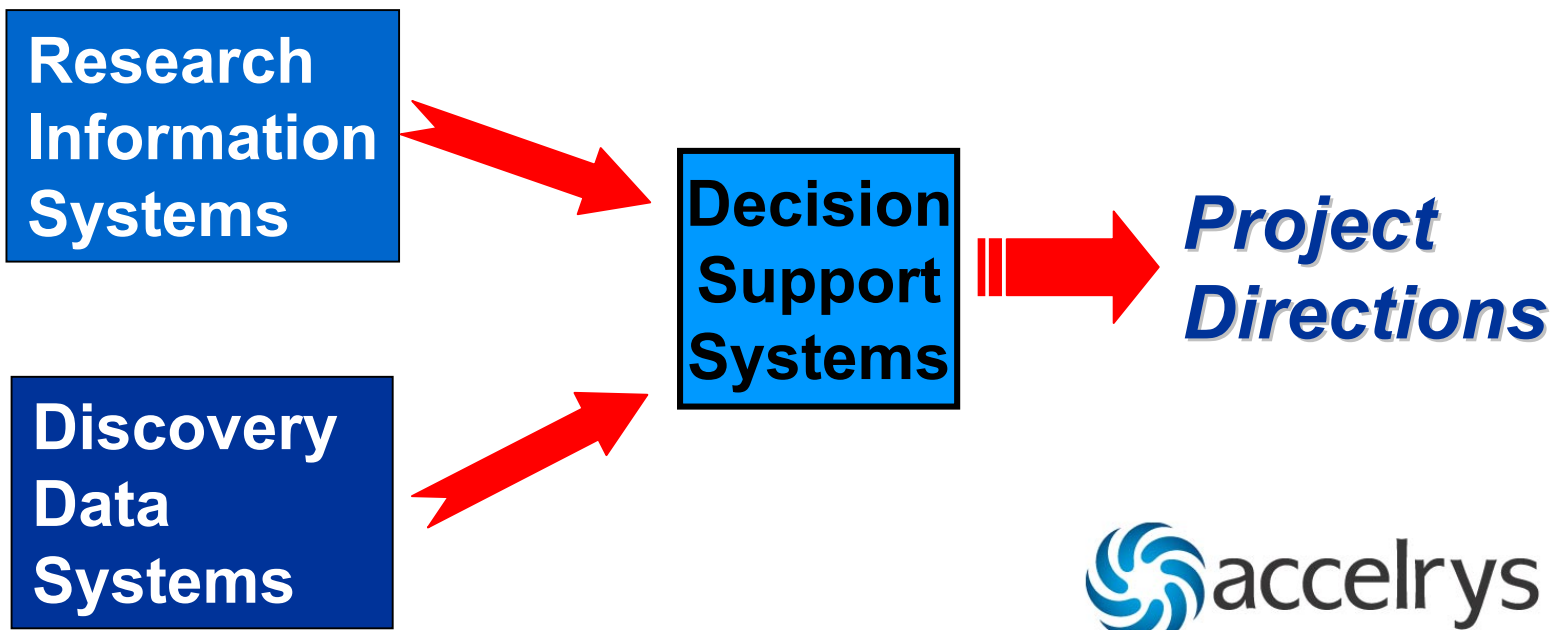
Some philosophy

Decision Support Systems

Definition: any system which enables the user to obtain all relevant information, analyze that information, perform "what-if" scenarios, and make better decisions about research directions and resource allocations



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Some philosophy

Decision Support Systems

- **Different system characteristics at different levels**
  - **"Personal" systems**
    - **personal, project, corporate, public information/data**
  - **"Teamware" systems**
    - **project data-in-progress**
  - **"Enterprise" systems**
    - **formal systems for capturing archival quality data**
- **Data ⇨ Information ⇨ Knowledge**
  - **Implies data tracking, data analysis, data extraction**

Some philosophy

Decision Support Systems Levels

DS System Level	Characteristics	Controlled by
Personal Systems	Desktop, open	Scientist
Team Systems	Desktop or client-server, more controlled	Group Leader, Project Administrator
Enterprise Systems	Controlled, secure, limited access	Data Administrator, Systems Administrator

Some philosophy

Molecular modeling by experts *vs.* molecular modeling by bench chemists

- **By computational chemists**
  - More theoretically defensible studies: better "science"
  - More through studies, more looking at alternative methods
  - Studies can result in improved methodology
- **By bench chemists**
  - Better, more timely integration of results into project flow
  - More "what if" scenarios, stimulates chemists thinking
  - Questions addressed more specifically to aid project
- **Best: joint modeling by experts and by bench chemists**
  - Useful division of labor for expert and chemists
  - Requires good methods of communicating results

Some current progress

Accelrys Systems Objectives

- **Personal, Team, and Enterprise Level Systems**
  - Cheminformatics, bioinformatics, simulation/computation systems
- **Tools for all Discovery Project Team Members**
  - Medicinal chemist, experimental biologist, molecular biologist
  - Computational chemist, protein crystallographer, spectroscopist
  - Group leader, data administrator, systems administrator
  - Methodology developer, systems developer
- **Meet needs at each level, enhance communication between levels and among disciplines**
- **Access all relevant information for best project decisions**
- **Enable customization, linkage to other apps**
  - Accelrys consulting, third parties, customers

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Some current progress

Desktop tools for the bench chemist

- **Chemist's spreadsheet:** ***Accord for Excel***
- **Chemist's database:** ***Accord for Access***
- **Chemically aware data analysis:** ***DIVA***
- **Property calculations, 3D structure analysis, SAR, pharmacophore model analysis, protein structure analysis, molecule docking, etc.:** ***MedChem Explorer***
- **Molecule viewing, comparison:** ***WebLab Viewer***
- **Library enumeration:** ***Accord for Excel Combichem add-in***
- **Toxicity prediction:** ***TOPKAT***
- **Others under development**

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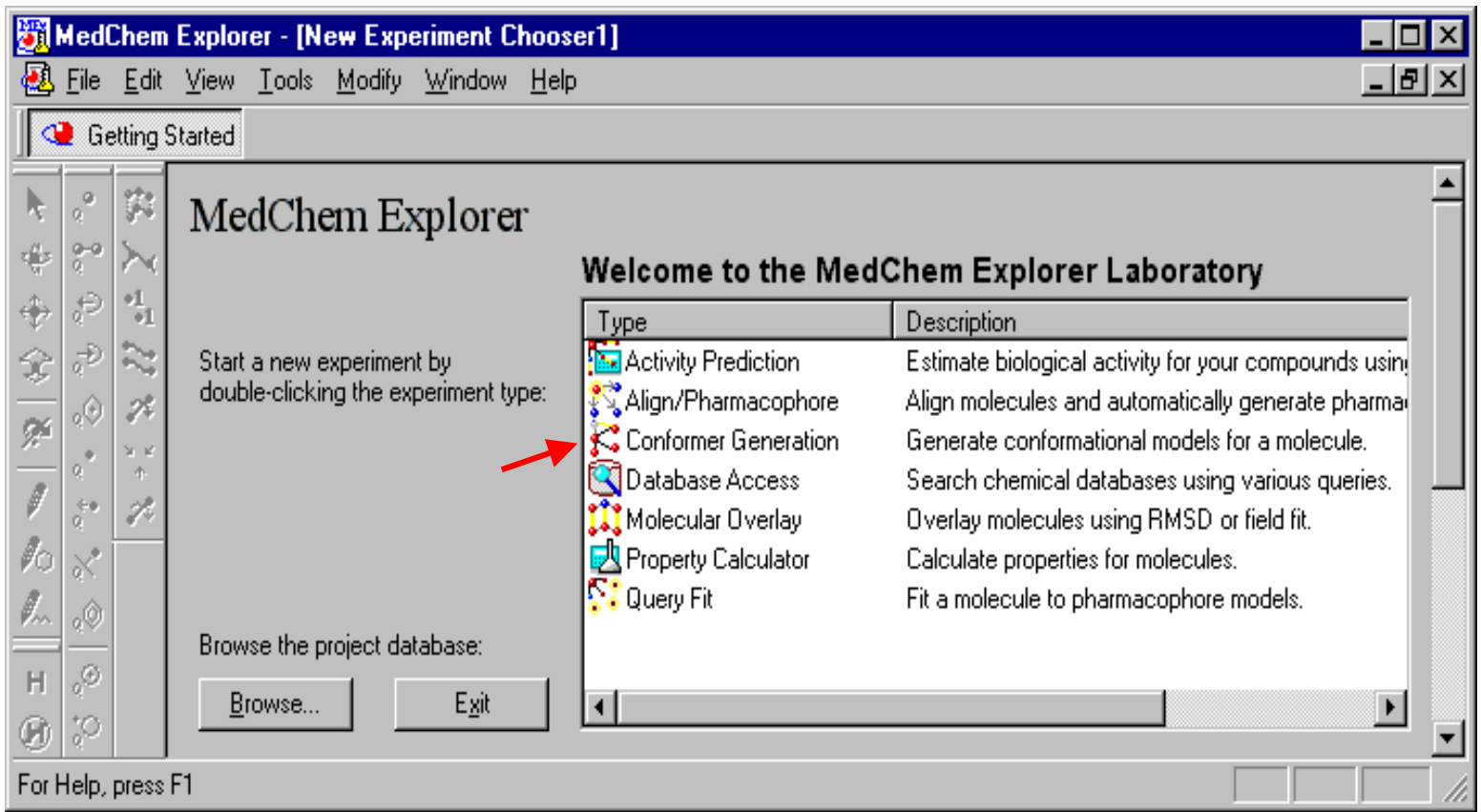
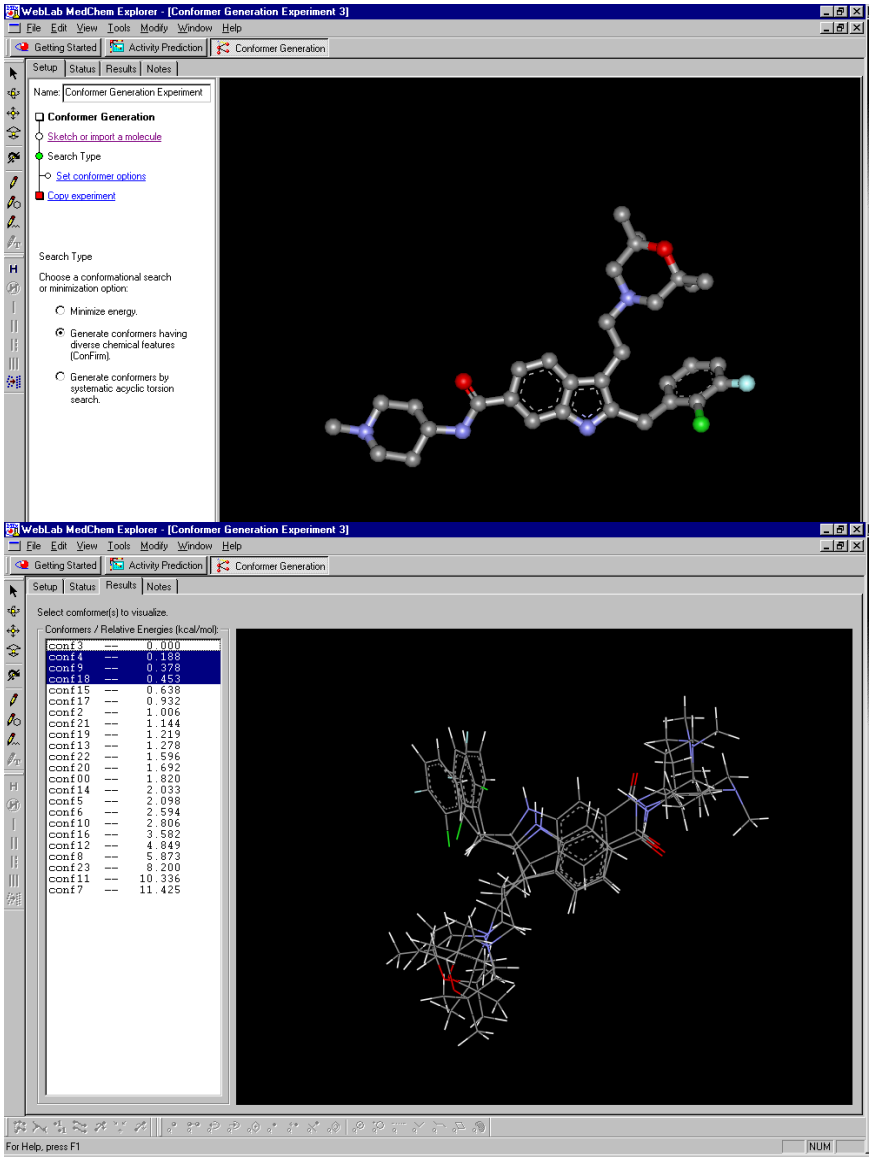
Some current progress

Applications for the project team

- **Project SAR tables:** ***Accord for Access, DIVA***
- ***Chemists' computational environment:*** ***MedChem Explorer***



MedChem Explorer Module Example: Conformer Generation



- Chemist-friendly energy minimization
- Calculation of diverse conformations
- Systematic conformational analysis
- Comparison of structures using other MedChem Explorer Modules
- Facilitates collaborative computational studies with project chemists and with modelers

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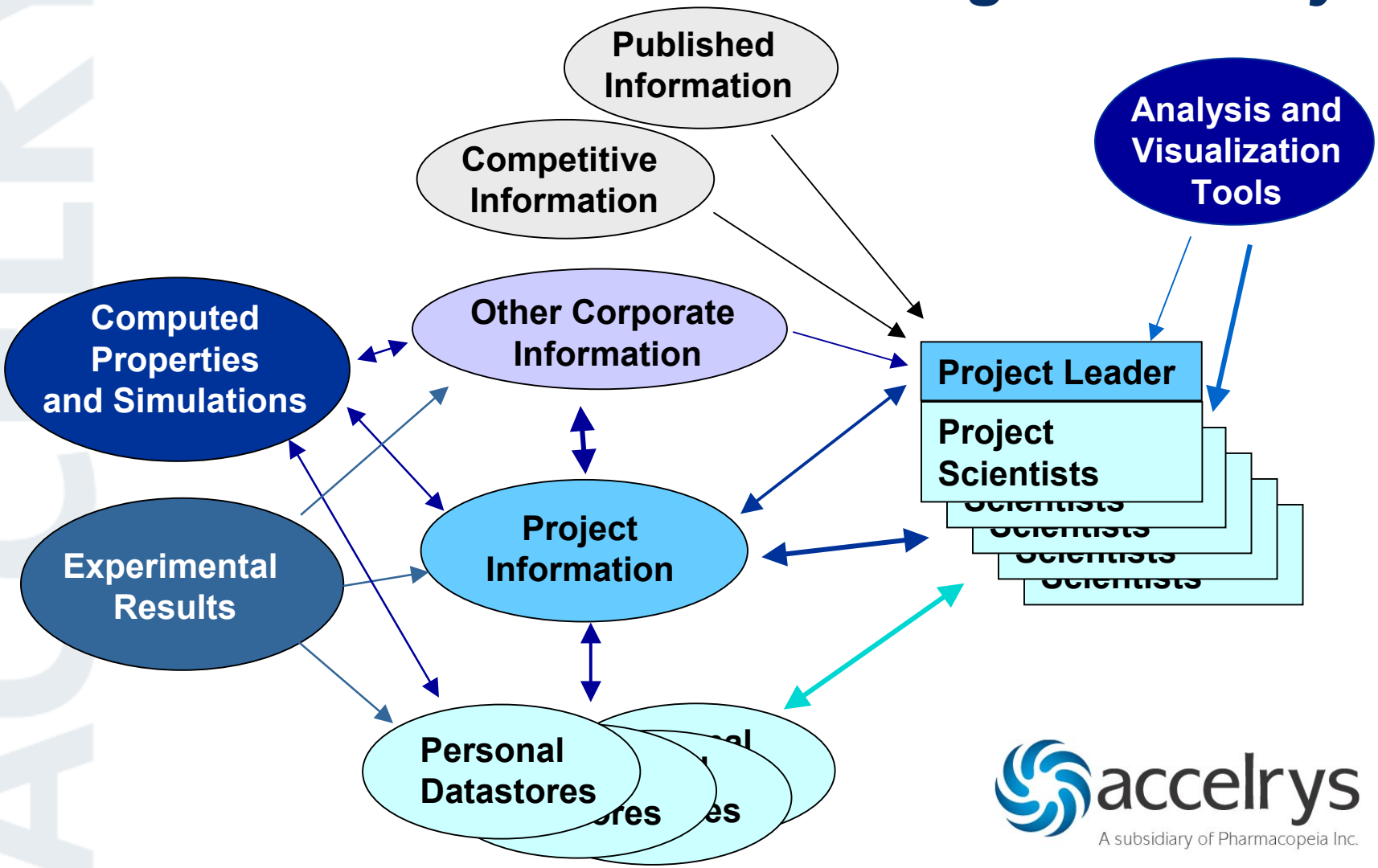
Some current progress

The Vision: *facilitated drug discovery*



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Some current progress

Decision Support Systems for the Practicing Medicinal Chemist: Summary

- **Medicinal chemist increasingly depends on computer applications to design, execute, and analyze experiments**
  - Including 3-D structures and properties, and simulation
- **Modern high-throughput discovery requires computer-assisted experimentation and analysis**
  - Commercial systems being built to meet these requirements
  - Transforming discovery from “cottage industry” to “HTD Team”
  - Informatics and computation make this possible

Ultimate payoff: more effective and efficient drug discovery!

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