MOLECULAR SIMULATIONS, INC.
(Formerly Biosym Technologies, Inc.)

Powerful Software for Designing New Molecules and Therapeutic Drugs

The traditional route to discovering new therapeutic drugs and other useful chemicals should probably be called "semiautomated serendipity." In the search for new drugs, hundreds of synthetic chemicals and natural substances are put through a long series of trials, starting with effectiveness tests in cell-based assays and concluding with toxicity and effectiveness trials in laboratory animals and, finally, humans. At each stage, the vast majority of substances fail the test and are discarded.

COMPOSITE PERFORMANCE SCORE
(Based on a four star rating.)
★ ★ ★

Using Mathematics to Find New Drugs

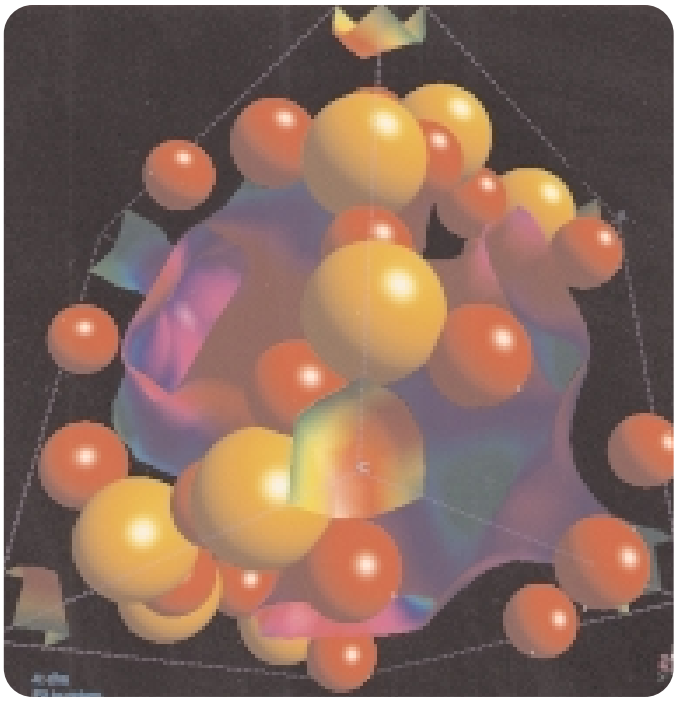
This ATP project with Molecular Simulations, Inc. (MSI), a small San Diego company that had 170 employees when the project began, combined applied mathematics and computer programming to develop new methods for simulating molecular structures and reactions. The technology is more efficient than conventional molecule-design techniques, a quality that translates into speedier product development and lower costs.

Density functional theory (DFT) proved as accurate as other approaches, yet much less expensive.

The ATP-funded effort led to new understanding of density functional theory (DFT), a quantum mechanics method. Most work to understand molecules is mathematical, and DFT is a relatively new form of applied mathematics previously not widely used to simulate molecules. Researchers successfully demonstrated the applicability of DFT to the study of biochemical systems, the backbone of drug research, showing that DFT is as accurate as other approaches and considerably less expensive.

Applications in New Drugs and Petrochemicals

Prior to its ATP award, MSI was already developing, marketing and supporting a suite of software tools suitable for computing the behavior and properties of molecules. The suite includes tools for bioinformatics, combinatorial library optimization, determination of protein structures



The geometrical and electron structure of a siliceous CHA-framework material isotopological with the mineral chabazite. Zeolites and related crystalline microporous solids such as chabazite have industrially useful separative and catalytic properties that are determined by both the micropore architecture and the nature of active sites.

PROJECT HIGHLIGHTS

PROJECT:
To develop density functional theory (DFT), a type of first principles quantum mechanics, for use in the development of new therapeutic drugs and other substances, an application that is expected to achieve substantial time and cost savings.

Duration: 6/1/1992 — 5/31/1995

ATP Number: 91-01-0224

FUNDING (in thousands):

ATP	$1,442	44%
Company	1,867	56%
Total	$3,309	

ACCOMPLISHMENTS:
MSI successfully demonstrated the applicability of DFT to the study of biochemical systems and developed software that employs DFT to efficiently calculate molecular structures and energies. The software was used to study biochemically relevant systems. It proved as accurate as other approaches, yet much less expensive. Also, the company:

- prepared more than 30 technical papers on the ATP-funded technology for publication in professional journals or presentation at conferences;
- implemented a highly accurate way of applying DFT in the company's Turbomole computer software product;
- expanded its physical plant to accommodate larger R&D and production facilities;
- was a finalist for a *Computerworld* Smithsonian Award, the 1996 Innovator Medal; and
- has grown at a cumulative annual rate of about 20 percent since the end of the ATP project in May 1995.

COMMERCIALIZATION STATUS:
Commercialization is in progress. MSI incorporated the ATP-funded technology into the company's existing Turbomole software package, which has been distributed to more than 100 sites. The ATP-funded technology has also been incorporated into MSI's quantum chemistry workbench software. Benefits from the ATP-funded technology are already accruing to users of MSI software, as well as to users of products developed with the software.

OUTLOOK:
Expectations for this technology and the company are strong. The technology has been incorporated into commercially distributed products that are being used extensively by a relatively small, yet global, community of scientists in academic, industrial, and governmental laboratories for rational drug design and petrochemical research. It has potential applications in biotechnology, microelectronics, and industrial fine chemicals research.

Composite Performance Score: ★ ★ ★

COMPANY:
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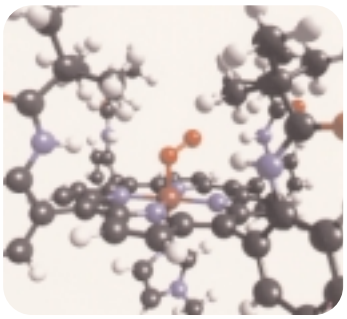
(MSI; formerly Biosym Technologies, Inc.)
9685 Scranton Road
San Diego, CA 92121

Contact: John M. Newsam,
Phone: (619) 546-5391
Number of employees: 170 at project start, 292 at the end of 1997



The geometry of a heme complex, optimized by first principles density functional methods implemented in the program DMol, using technology developed under ATP sponsorship. In this molecule, which contains more than 150 atoms, the central iron atom (central, dark red) is coordinated by four nitrogen atoms (blue) of the heme group, and a dioxygen molecule (red).

from amino acid sequences, and structure- and analog-based rational drug design. The ATP project enabled MSI researchers to incorporate the new DFT knowledge into several of these tools. Most MSI software users benefit from access to several different tools and will use more than one of them in a given study.

One of the first MSI tools to be enhanced with the DFT technology was Turbomole, a computer software application that integrates a database of atomic functions, a modern user-interface, and mathematical tools like DFT. The computer program calculates tables of molecular characteristics and generates a three-dimensional structure of the molecule that can be viewed by molecular graphics.

Another tool upgraded with the new technology is DMol, a quantum chemistry program that enables users to make reliable, quantitative predictions about molecular systems. The ATP-funded technology—a DFT-based component of the program—decreases the cost of these types of computation, potentially reducing the cost of designing new molecules. The ATP-funded technology is being used experimentally in petrochemical research, and it has potential applications in biotechnology, rational drug design, microelectronics, and industrial fine chemicals research.

Researchers successfully demonstrated the applicability of DFT to the study of biochemical systems, the backbone of drug research . . .

Benefits to Companies and Consumers

Because the MSI software is relatively low-cost, enters the discovery and development cycle close to its beginning, and is used by research and development personnel in large organizations, the benefits to the users of the software can be large relative to what MSI earns through software licenses. Such benefits will accrue to chemical, petrochemical, pharmaceutical, and biotechnology companies, as well as to companies in other industries that use MSI software incorporating the ATP-funded technology. Benefits will also accrue to people who use therapeutic drugs and other products made by companies using the new technology. In addition, scientists worldwide might benefit from a database of molecular structures developed under the ATP award — MSI is considering making the database available on the Internet.

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. . . potential applications in biotechnology, rational drug design, microelectronics, and industrial fine chemicals research.

MSI reports that the ATP funds enabled it to complete research on the DFT technology and incorporate the results into its software products some 18 months earlier than it would otherwise have been able to do. The company, its customers in the pharmaceutical and materials industries, and their customers have all benefited. The project also facilitated the dissemination of new knowledge, particularly via the many scientific papers that were published about the ATP-funded technology.

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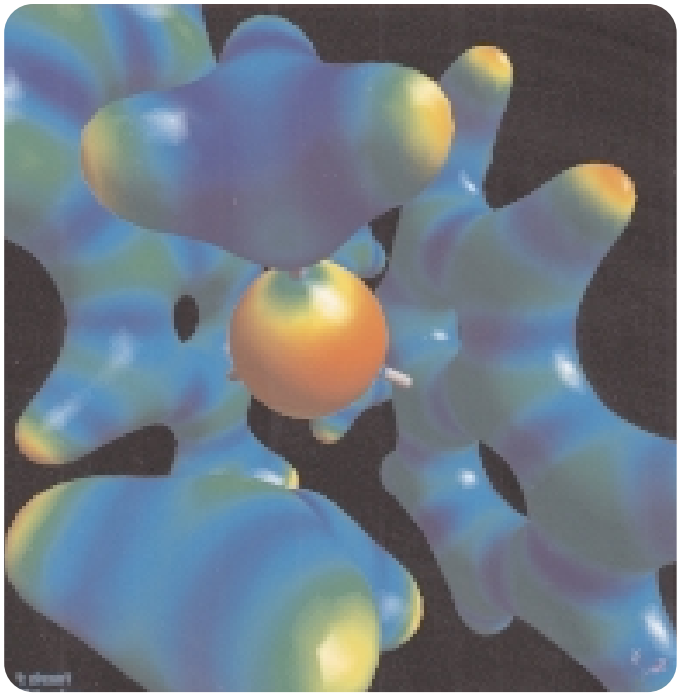

Electron density isosurface of a zirconocene complex, color-coded by electrostatic potential, as computed by the DMol program. The geometrical and electronic structures in metallocene complexes govern the nature of the polyolefin products produced when single site catalysts of this type are used to catalyze olefin polymerization.

Company Grows, Announces IPO, is Acquired at a Large Premium

Since the end of the ATP project in May 1995, the company has grown at a cumulative annual rate of about 20 percent. In February 1997, it filed a Form S1 with the Securities and Exchange Commission announcing its intention to conduct an Initial Public Offering of stock, and noted that it expected to raise about $35 million by selling about half of the stock in the company. In February 1998, the company and Pharmacopeia, Inc., announced that Pharmacopeia would acquire MSI. The acquisition was finalized in June 1998 in a transaction valued at approximately $140 million.