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An early history of the molecular modeling industry

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The results of molecular modeling studies appear in nearly every scientific publication dedicated to compound discovery. How did the companies that make these products start and evolve? Where did the science contained in these programs arise?

In 1961 James Hendrickson used the early concepts of a force field and an IBM 709 computer, capable of '8000 additions or subtractions, 4000 multiplications or divisions or about 500 more-complex functions (powers, roots and trigonometric functions) per second', to calculate the conformational energies of cycloheptanes. In 1966 Cyrus Levinthal extended the idea of utilizing computers in chemistry when he published work detailing the use of molecular graphics and computer simulation to study the structures of proteins and nucleic acids. These events inspired several groups to initiate work on modeling systems and advances in computer technology, graphics techniques and algorithm development facilitated the creation of a specialized industry dedicated to modeling the structure and properties of complex molecular systems. While this industry began in 1978 with the formation of two companies, between 1978 and the present it grew from a niche market where a handful of companies struggled to remain viable to one that is made up of over 20 diverse firms, collectively earning hundreds of millions in revenues. The growth of this industry over the past 30 years will be examined in this review. In particular, the migration of research from academic groups to the commercial marketplace, the influence of the customer base and the impact of business analysis and segmentation studies on product directions will be investigated.

Molecular modeling in the chemical industry

The origin of computational chemistry (as well as the definition of the field) has been the subject of several discussions [1], although Heisenberg's 1925 paper on the theory of quantum mechanics [2] is considered to be the first publication in the field. In 1961 James Hendrickson demonstrated that computers could be used to calculate molecular energetics [3,4], and Cyrus Levinthal later added the dimension of visualization [5]. However, examined from a practical perspective, the origins of computational chemistry stemmed from the desire to understand the relationship between structural features and observed properties, and the need to use these relationships to improve compound activity/property profiles.

During the late 1960s and early 1970s computational-based efforts began to evolve within several chemical industry segments. In these newly formed groups, scientists from a variety of disciplines were tasked with developing experimental design and structural analysis tools that were based on the latest research in physical–organic chemistry and advances in computer system design. One impact of this work was that, in many of these companies, in-house systems would effectively limit the market for the commercial programs that would appear during early 1980s.

One of the first companies to undertake the application of computational analysis was Eli Lilly. During the mid-1960s Max Marsh and Robert Hermann utilized Hermann's Extended Hückel theory program and an IBM 7094 that was housed at the General Motors facilities in Speedway, Indiana to calculate properties that were used in statistical analyses of activity. At Smith Kline and French, Richard Cramer, a recent post-doctoral student who worked on the LHASA project under the direction of Corey *et al.* [6–8], established the computer-aided design program during 1971. Cramer's work focused on his interest in the use of statistics to analyze biological activity [9,10]. Other members of the Corey/LHASA project who spearheaded the early growth of computational chemistry during the early 1970s included Jeff Howe (who joined Upjohn in 1974 and initiated the development of the Cousin cheminformatics project with Tom Hagadone), David Pensak (who joined DuPont in 1974) and Todd Wipke.

In addition to an extensive early body of work [11], Wipke's influence on the early growth of molecular modeling was extended by the work of the scientists he trained at his molecular

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sciences research laboratory at Princeton University. In 1973 Tom Dyott left Wipke's lab to join with Rob Koller to build the computational group at Rohm and Haas. The techniques that were initially developed included the use of molecular descriptors and pattern recognition, which culminated in the development of the MOLY program [12,13]. During the same year, Peter Gund joined the research department at Merck where he initiated the development of the Merck Molecular Modeling System with Graham Smith, Bruce Bush and Joseph Andose [14]. Major sections of this system were originally developed on an IBM 370 using Tektronix 4010 and GT42-GT43 display systems [15]. And, in 1974, Clark Still, a postdoctoral fellow, left the group for a postdoctoral fellowship with Gilbert Stork at Columbia University; in 1977 he would return to the department as a professor.

Where the research program in Wipke's laboratory emphasized methods of structure handling and analysis, Corwin Hansch, a research professor at Pomona College, focused on the applications of regression techniques to the correlation of structural properties and biological activity [16–19]. During the late 1960s and early 1970s Yvonne Martin, following discussions with Hansch, began to develop and apply the methods of regression analysis to compounds at Abbott. By 1975 she expanded these efforts by utilizing Tony Hopfinger's software [20] and the XRAY analysis program that was developed by Richard Feldmann [21,22]. The programs ran on a DEC-10 and utilized the GT-40 and Tektronix display systems. By 1980 the program had grown to six people who were devoted to computer-aided drug design and the development of their in-house system, CMD.

Hansch also directly trained several scientists who would become prominent in the computer-assisted molecular design industry [23,24], including David Weininger and Albert Leo, who would utilize research from the Pomona MedChem project as the basis for the formation of Daylight Chemical Information Systems. During this period, Lamont Kier formalized Ehrlich's original definition of the pharmacophore [25] and described the application of concept in his publications [26,27], which influenced the development of a large number of commercial software and pharmaceutical company modeling algorithms [28,29].

Early analytical chemistry and experimental design scientists also contributed to the growth of computational chemistry. The techniques utilized during this period were collectively grouped in the discipline of chemometrics [30] and represented new applications of artificial intelligence to structure recognition and categorization. Research groups headed by scientists such as Thomas Eisenhour, Bruce Kowalski and Svante Wold published new approaches to chemistry and trained the group of graduate students who would move these techniques into more direct applications in computational chemistry. In 1969 one of the first of these newly trained informaticians, Peter Jurs, joined the faculty at Pennsylvania State University where he initiated a research program that would result in the development of the ADAPT (Automated Data Analysis using Pattern Recognition Techniques) program [31], as well as training several students who would assume leadership roles in the pharmaceutical and molecular modeling industries.

In 1965 Bruce G. Buchanan and Edward A. Feigenbaum initiated the DENDRAL project at Stanford University to examine the use of symbol manipulation and artificial intelligence in domain-specific fields of science [32–34]. During the late 1970s two of the members of this effort, Ray Carhart and Dennis Smith, completed their work with Carl Djerassi [35–37] and joined the growing computational efforts at Lederle Research, while another member of the group, Jim Nourse, became one of the first members of the chemical database company Molecular Design Ltd. Carhart and Smith would later migrate to MDL as well. The work within the DENDRAL project team also led to the creation of some of the early commercial computational chemistry programs, including CONGEN and GENOA [38].

While computational chemistry was spreading within the chemical industries, several government research laboratories also initiated systems development efforts relating to crystallography, molecular graphics and data storage. In 1970 crystal structures for hemoglobin, myoglobin, papain, subtilisin, carboxypeptidase, chymotrypsin, lysozyme and ribonuclease were available for research analysis. However, as the number of solved structures began to increase, the community found that they needed to provide a curated, central storage facility for these structures. The Protein Data Bank was created in 1971 at the Brookhaven National Laboratories in response to this need [39,40]. This was soon followed by the creation of a repository for 'small molecules' with the creation of the Cambridge Crystallographic Data Centre in the UK [41,42]. In 1974 the NIH published details of a new molecular modeling system that was available for the research community, the NIH Prophet system [43]. Bolt, Beranek and Newman wrote and supported the software for Prophet as contractors. The system was run on a DEC PDP-10 computer that was accessed using modems attached to Tektronix 4010 graphics terminals.

Molecular graphics

As the fundamentals of quantum chemistry were being codified into useable programs and algorithms [44–50], advances in computer technology facilitated the evolution of the graphics systems and standards that would permit chemists to view and manipulate the results of their calculations in real time. While the first efforts to utilize computers for the display of molecules were part of the Mathematics and Computation (MAC) project at MIT [51], members of this group and computer scientists in Europe were able to extend the initial research rapidly. During the mid-1960s David Barry left the MAC project and joined scientists at the Computer Systems Laboratory at Washington University School of Medicine where the group developed the molecular graphics techniques that were used with Garland Marshall's MMS-X molecular modeling programs [52–54]. By 1978 Alwyn Jones published the details of his general-purpose macromolecular modeling and refinement program FRODO, which ran on the PS2 and the newly released Multi Picture System (MPS); a color, vector-based graphics systems from Evans & Sutherland [55].

As Evans and Sutherland continued to increase the performance of their graphics systems and introduced the color PS300 series of graphics systems, newer programs with more sophisticated capabilities began to appear including GRIP [56,57], TRIBBLE [58], GRAMPS (Graphics for the Multi Picture System) [59], GRANNY (the program that told GRAMPS what to do and how to behave) [60], MIDAS [61,62], GRINCH [63], GRID [64], MOGLI (Molecular Graphics Library, which was renamed PSShow by Evans and Sutherland) [65], Insight [66] and HYDRA [67]. During the period when advances were made in graphics programming and display,

computer hardware was also becoming increasingly smaller and more powerful so that, by the beginning of 1980s, it was possible to purchase a VAX minicomputer and an Evans and Sutherland graphics head, although the cost of this equipment was roughly equal to the price of a moderately sized mansion.

The creation of the molecular modeling industry

Given the interest in molecular modeling and the desire within the chemical industries to extend this technique, it was not surprising to find that individuals within the leading academic and government centers for computational research were sought as consultants. However, it was not until 1978 that a portion of the research directed toward computer-assisted modeling was turned into the first commercial organization. Molecular Design Ltd (MDL) was founded in California by Stuart Marson, Steve Peacock and Todd Wipke. Marson, who had completed his PhD at Stanford, and Peacock were postdoctoral fellows at Berkeley. Wipke had recently moved to UC Santa Cruz. The company started as a computer-aided molecular design consulting company that used the computational tools developed by Wipke and other academicians. However, based on their customers continued requests to access their tools for proprietary research, the company began offering a product line that included MACCS (The Molecular ACCess System), Tony Hopfinger's ChemLab program, PRXBLD, ORTEP, CONGEN and Allinger's MM series. The software ran on Prime computers and Tektronix-type display systems, although it was quickly migrated to VAX computers during the early 1980s. Chevron, Shell and FMC Corporation were the company's initial customers. Over the next four years, the company's product line became focused on chemical database technologies and in 1982 it discontinued marketing molecular modeling tools and introduced REACCS (Reaction ACCess System), the first commercial database systems for managing information related to chemical reactions.

In 1979 Garland Marshall also looked at the requests being made of his research group and their approach to computer-aided molecular design [68]. However, pharmaceutical groups who were interested in exploring the application of the software felt that the equipment needed to run the program was expensive and that the techniques encoded were unproven to most medicinal chemists. In addition, companies, even though interested, were not willing to undertake the support of spaghetti code written by academicians. It was the realization that an organization was needed to provide support, maintenance, training and enhancements that led to the incorporation of Tripos Associates in St. Louis. The company's product was SYBYL, which ran on the Gould SEL minicomputer with customer graphics hardware. The company's first customers included Searle, Smith Kline French, Ayerst, Pennwalt, The University of Strasbourg and Nelson Research. For the first few years, a small staff of scientists and programmers supported these six customers.

Given the wealth of algorithms available, the examples of MDL and Tripos, the advances in graphics techniques that had been made and the need to reduce the cost of compound discovery it was not surprising that 1980s saw the rapid growth of the molecular modeling industry. During this decade scientists from a range of disciplines founded 18 companies in the USA and Europe.

The first such company of 1980s, while not a molecular modeling company, was Hare Research. Dennis Hare formed the company during 1982 to address the market for NMR data management and structure refinement software. The primary products were FELIX, an NMR data collection and management program, and the structure refinement program DSPACE, which used the principals of distance geometry to calculate 3D structures for proteins [69,70]. The following year Keith Davies, a Junior Research Fellow with Graham Richards at Oxford University, and his sister Mary formed Chemical Design Limited (CDL) in the UK. In 1984 CDL's 'official' office was opened and a VAX computer was ordered for software development. The original product, Chem-Graf (later renamed Chem-X) combined molecular mechanics, conformational analysis and molecular graphics using data structures designed for the full 32-bit VAX architecture with molecular graphics handled by Sigmex raster graphics terminals.

Up to this point, commercial molecular modeling was primarily built on the combination of molecular mechanics and molecular graphics. The companies that were formed during 1984 changed this landscape significantly by extending into the field of protein simulations. The first company, BioDesign, was founded by William Goddard and two of his former graduate students, Stephen Mayo and Barry Olafson. Mayo had developed new approaches for visualizing proteins and Olafson utilized experience in molecular mechanics and dynamics gained as a postdoctoral fellow in Martin Karplus' group [71] to examine new approaches to force fields. The software was developed on a VAX that was hooked to the new Evans and Sutherland PS-300 graphics system. BioDesign's initial customers, including Eastman Kodak and Glaxo, were supported by Olafson, Mayo and another Karplus student, Wally Reiher, who came into the company from the biotech industry.

On the east coast, Frank Momany, Jeffrey Wales, Jean-Loup Fayolle and Andy Ferrara created Polygen, a company whose product was the commercial version of CHARMm linked to Quanta, a graphics program, which was the commercialized version of HYDRA. Momany, a graduate student from Harold Scheraga's lab, came to Polygen from academia and Wales joined from Digital Equipment Corporation. Ferrara, a former VP at Eli Lilly, was the person responsible for licensing CHARMm from Harvard University. The company started with 6–12 people (three of whom were computational scientists) and was initially funded by a contract with Kodak. Later customers included Nutrasweet, Pfizer and Merck; by 1986 the company had grown to 20 people.

On the west coast, Arnold Hagler and Donald MacKay founded Biosym Technologies. Biosym's first product, Discover, was based on the force field and molecular dynamics work by Hagler and Lifson [72–75] and was coupled to the Insight molecular graphics system that was developed by Dayringer. The final computational chemistry group that appeared in 1984, while not a stand-alone company, was the Molecular Sciences Group within Evans and Sutherland. The group was headed by Eric Swanson and offered a variety of software including Robert Pearlman's Concord [76,77], Andrew Dearing's MOGLI and Richard Boyd's polymer modeling programs [78].

As these new computational tools became available, industry expanded its use of molecular modeling. Companies including Glaxo, Parke-Davis, Ciba-Geigy, Searle, Astra, Zeneca/ICI, Ayerst, Lederle, among others added scientists whose responsibility was to build a computational component into the research effort.

However, the early hardware available to these groups limited their ability to perform their jobs in an efficient manner.

At Glaxo, for example, Peter-Murray Rust was provided with a used PDP-11 and one of the Tektronix 4010-based graphics terminals. The equipment was upgraded to a VAX-750 and Megatek color graphics display during the first or second year; however, the reliability of the graphics system made it difficult to develop and display models to the chemists. The group found that the graphics controller was sensitive to cold and would draw calligraphy traces instead of straight-line vectors when it was used after being turned off over the weekend. Despite these limitations the computational group was able to introduce interactive 3D into research.

The mid-1980s also marked an interesting point in the evolution of the molecular modeling marketplace. Several of the established modeling groups within industry were refining their in-house software. For example, Abbott rolled out an integrated cheminformatics program, SWAMI and initiated development of their 3D structure searching and pharmacophore identification programs, ALADDIN [79] and MENTHOR [80]. Merck, DuPont and Rohm and Haas also continued to add functionality to their in-house modeling tools. As these expanded systems were introduced, the barrier to entry for commercial software increased. However, as the systems grew in complexity the support requirements also increased to the point that senior management began to question the value that the company obtained relative to their costs.

On the commercial side, Glen Hopkinson founded the chemistry-reaction database company ORAC Ltd. Their ORAC and OSAC products were the first direct competitors for the MDL suite of chemistry database systems and the appearance of this company served notice that the niche markets that each of the companies assumed they owned were about to become competitive. In addition, molecular modeling software written for the IBM personal computer and the Apple Macintosh made its first commercial appearance.

The first established company to offer PC-based modeling software was Tripos, which marketed Alchemy, a modeling system for the NEC personal computer, and Nitro, a PC and Macintosh-based terminal for SYBYL. In 1985 Hypercube was founded by Neil Ostlund; the company's product, HyperChem, was one of the first computational programs to run on the IBM PC. Serena Software, incorporated by Kevin Gilbert, offered the PC-based software GMMX and PCModel. During the following year, brothers Stewart and Michael Rubenstein founded Cambridge Scientific Computing (later named CambridgeSoft). Their company marketed the first Macintosh-based programs for structure drawing and molecular modeling. CAChe Scientific, established by George Fabel and George Purvis as a subsidiary of Tektronix, also offered MacIntosh-based computational chemistry and display programs. By the end of 1986, 18 companies marketed software dedicated to molecular modeling, cheminformatics and chemical registration and documentation.

Concluding remarks

By the mid to late 1980s interest in the promise of computer-aided drug design was being discussed outside of the community. Several articles appeared in the popular press and many business analysts were developing scenarios that demonstrated the ways in which computer modeling could save the pharmaceutical industry significant portions of the cost of developing new therapeutics. As a result of this level of interest in computational approaches to research, the number of startup computational chemistry companies continued to expand. During 1987 five new organizations joined the growing list of molecular modeling companies:

- Biostructure SA was founded by Jean-Marie Lehn, Bernard Roques, Dino Moras, Pierre Oudet and Gerard Bricogne.
- Daylight Chemical Information Systems was incorporated by David Weininger and Yosef Taitz.
- Gaussian was founded by John Pople.
- Proteus Molecular Design was created by Kevin Gilmore, John Pool and Barry Robson.
- Columbia University began distribution of Clark Still's MacroModel program [81].

In 1989 the growth of the market showed no signs of slowing, as evidenced by even more companies joining the field:

- BioCAD Corporation (Terry Smith, Michael Jacobi and Steve Teig)
- Cambridge Molecular Design (Patrick Coulter).
- Oxford Molecular Group (Anthony Marchington, David Ricketts, James Hiddleston, Anthony Rees, and Graham Richards).

By the beginning of 1990 over 25 independent companies were part of the computational chemistry community and their products were in use in nearly all of the major pharmaceutical and chemical companies throughout the world. While the growth of this industry segment over a short 20-year period was impressive, several market forces were developing, some of which came as a surprise to the vendor community. The impact of these changes in the business climate will be examined in the second part of this issue.

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