University of California, San Francisco

The coming of desktop molecular modeling

The practice of chemistry inhabits a strange twilight world between the abstract and the real. The basic building blocks of matter are hidden from the chemist's eye; yet matter itself is tangible and visible to us all. Chemical knowledge derives from the chemist's preoccupation with building models in an attempt to visualize the invisible. An exciting modeling technology that utilizes sophisticated software running on computer graphics workstations heralds a new era of visualization for the chemist. Some of the potential of this new world of molecular modeling is demonstrated by a software application called MidasPlus, created by scientists and programmers at the School of Pharmacy at the University of California, San Francisco (UCSF), under the direction of Tom Ferrin and Robert Langridge.

ªChemists have always been better at understanding molecules when they can see a three-dimensional model, look at it from different angles, and even move parts of it around,º observes Tom Ferrin, adjunct professor in the Department of Pharmaceutical Chemistry and director of computing at the Computer Graphics Laboratory. ªThere's some understanding process that happens when they can manipulate molecular structures.º

ªPhysical models, made from colored balls and wire, work well for small structures,º he continues, ªbut as the models grow larger and larger, they become fragile and unwieldy. So there's a lot of advantages to modeling molecules in a computer, doing all the manipulations on the graphics display. And, if you're going to transfer that process to the computer, interactive color graphics are critical.º

Inside the MIDAS touch

The Molecular Interactive Display and Simulation (MIDAS) System is a collection of programs developed by the Computer Graphics Laboratory in the early 1980s. MIDAS originally ran on three-dimensional graphics display terminals attached to host computers. The primary component is MidasPlus, an interactive graphics program for the display and manipulation of large molecules such as proteins and nucleic acids like DNA. In 1989, MidasPlus was rewritten to work with new color graphics workstations.

MidasPlus starts with a profile of a molecule acquired from other software tools that perform computations based on information gleaned from crystallization experiments. MidasPlus can show a molecule as a stick-figure image, in which lines represent atomic bonds, and the intersection of lines, atoms; as a ribbon image, in which parts of the molecule are displayed as geometric shapes, such as helices and planes or sheets; and as a conic image, in which each atom is represented as a three-dimensional ball stuck together with other balls. In all of these views, the molecule can be oriented in any position.

The stick-figure imaging can be particularly rich in information. A part of the molecule can be selected for

investigation, and magnified; labels can be displayed indicating the atom type and its electrostatic charge. The distance between atoms can be measured in angstroms, and dynamically altered with the mouse. Surface representations of the atoms can be illustrated with van der Waals surfaces.

Introducing MidasPlus to the NeXT environment
When MidasPlus was rewritten, the code was designed with portability in mind. A layer of three machine-dependent software modules was inserted between the computer and the main application program; porting became an exercise in creating these three modules for each specific platform. The bulk of MidasPlus-about 85 percent of the total source code-is written in the C programming language, and transferred to the NeXT environment with little or no change. Greg Couch, a programmer in the Computer Graphics Laboratory, learned Interface Builder and the Application Kit™ to develop the machine-dependent code.

ªGreg completed the port over an eight-month period, and he had several other responsibilities at the time,º Ferrin says. ªWe estimate that it took the equivalent of four months of full-time work-and that includes learning Interface Builder and the details of NeXTstep. I'm pleased with the results.º Ferrin, Couch, and the other programmers in the Computer Graphic Laboratory have been so taken with the NeXT development tools that they have made NeXT computers their development platform of choice.

ªI'm impressed with Interface Builder,º Ferrin says, ªand we've already developed several applications that are unrelated to MidasPlus. For example, we developed a program for monitoring our network-and each of its different subnetwork segments-that interfaces with a device called an EtherMeter. One of our programmers, Conrad Huang, developed it while we tracked how long he worked on it, and it's fair to say it took half the time to develop that application on a NeXT computer than it would have in an alternative development environment.º

Desktop molecular modeling on every workbench
But it is the implementation of MidasPlus on the NeXT computer that has really inspired Ferrin, as he articulates a vision of affordable computer modeling for every chemist.

ªUntil now, if you wanted a 3D color graphics workstation, the least expensive and smallest computer you could buy would be one of the Silicon Graphics IRIS machines,º he explains. ªA reasonable configuration costs $20,000, and you can easily spend $40,000 if you add high-performance graphics, high-capacity disk drives, tape drives, and stereo viewing peripherals. You can't afford to put one of those on every chemist's workbench; yet clearly, the capabilities of computer modeling would be beneficial to virtually every chemist. NeXT computers provide the potential to put interactive molecular modeling on every chemist's bench. We like to call it `Desktop Molecular modeling'.º

The productivity benefits are obvious. Currently, even in a computer-rich environment like the UCSF Pharmaceutical Chemistry department, researchers must share IRIS workstations for modeling work. With a workstation on every chemist's bench, waiting for computer time would become a thing of the past. In addition, a multi-window workstation environment, such as that provided by NeXTstep, will let chemists access all of the tools of a multimedia working environment-word processing, database query, graphics, and now interactive

molecular modeling. It's the technological capabilities available in higher education today that lend credence to Ferrin's vision of the future.

ªI'm excited about NeXT's commitment to higher education,º he says. ªTools like MidasPlus and the NeXT computer are becoming more pervasive in our department. As we train tomorrow's scientists to use these tools, they will radiate out to pharmaceutical companies and other research institutions and convince others that they could be more productive with these tools.º

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