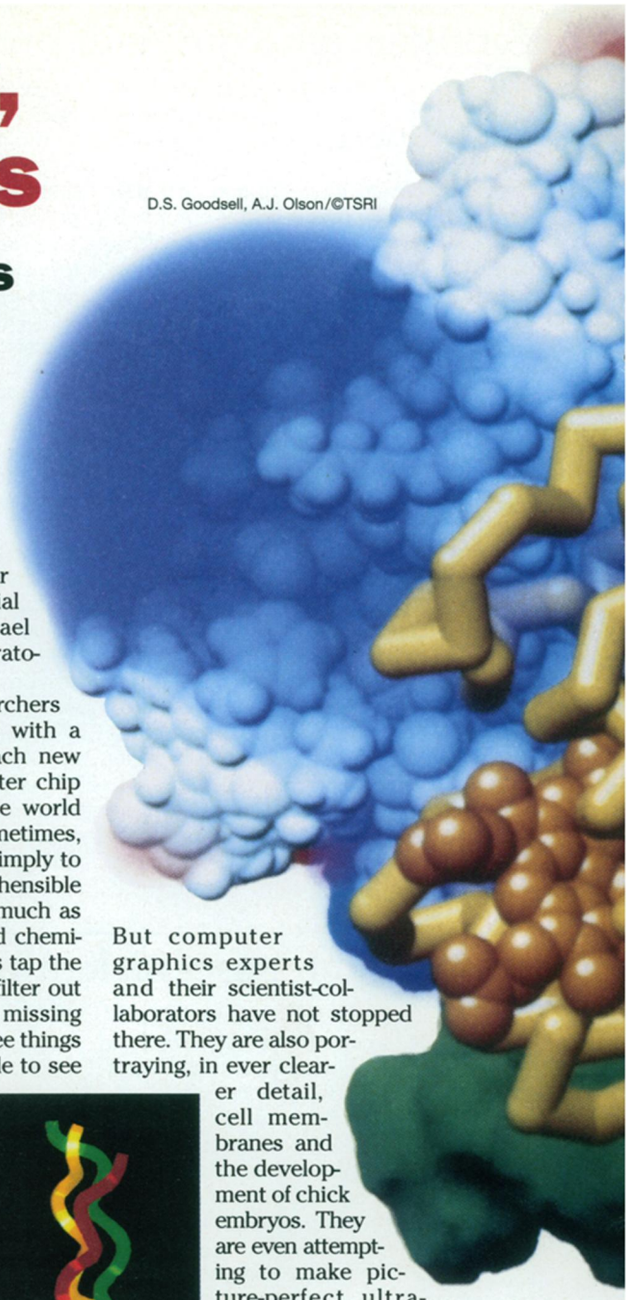
Twirling Ribbons, Billowing Bubbles

Computer visualization brings complex aspects of life into view

By ELIZABETH PENNISI



D.S. Goodsell, A.J. Olson/©TSRI

It's no big deal to sketch a water molecule, with its two hydrogen atoms linked to an oxygen, or to picture how those atoms interact with another substance. But when molecules contain hundreds or thousands of atoms, even a brilliant chemist has trouble keeping them all straight, never mind tracking how each atom moves or changes when confronted with other molecules.

Nor does the challenge end with molecules. Researchers, teachers, and physicians want to compile the massive amounts of data acquired through various imaging and analytical technologies in order to make and manipulate clear pictures of cells, organs, even entire organisms.

That's where computers, particularly computer graphics, come in. By incorporating computational and visualization techniques into their experimental repertoire, researchers can make sense of ever more complex data and substances. X-ray crystallographers, for example, have demonstrated that amino acids, the building blocks of proteins, form chains that twist into incredibly convoluted configurations, or motifs. Sometimes these structures are shaped by other, helper molecules.

Jordi Bella *et al.*/SCIENCE

A: Collagen's blue, purple, and green amino acid strands with the alanine substitute in yellow.

"But from my point of view, that's just the beginning," says Arthur J. Olson of the Scripps Research Institute in La Jolla, Calif.

Like other computational chemists and molecular biologists, Olson has built on those data and, with certain mathematical procedures, has reenacted molecular minglings. "That's really the crucial aspect of biology," adds Michael Colvin of Sandia National Laboratories in Livermore, Calif.

As part of these efforts, researchers have become artists, sketching with a keyboard instead of pastels. Each new line of computer code, each faster chip has brought a little more of the world beyond our vision into view. Sometimes, the scientists ask the computer simply to compile all the data into a comprehensible picture, one based totally, or as much as possible, on existing physical and chemical laws. Other times, researchers tap the computer program's intuition to filter out unimportant data and fill in missing details. "[Visualization] lets you see things that you might not have been able to see before," says Helen M. Berman, an X-ray crystallographer at Rutgers University in New Brunswick, N.J.

Berman remembers the early days of computer graphics, when images came only in black, white, and shades of gray. "I thought, What do we need color for? It's just a luxury," she recalls. Now, she realizes how much better colors are at capturing the personalities of molecules. The bright blues, yellows, and purples help experts as well as novices make sense of what sometimes seems little more than a tangled mess of squiggles or — in the case of ultrasound data — a fuzzy image.

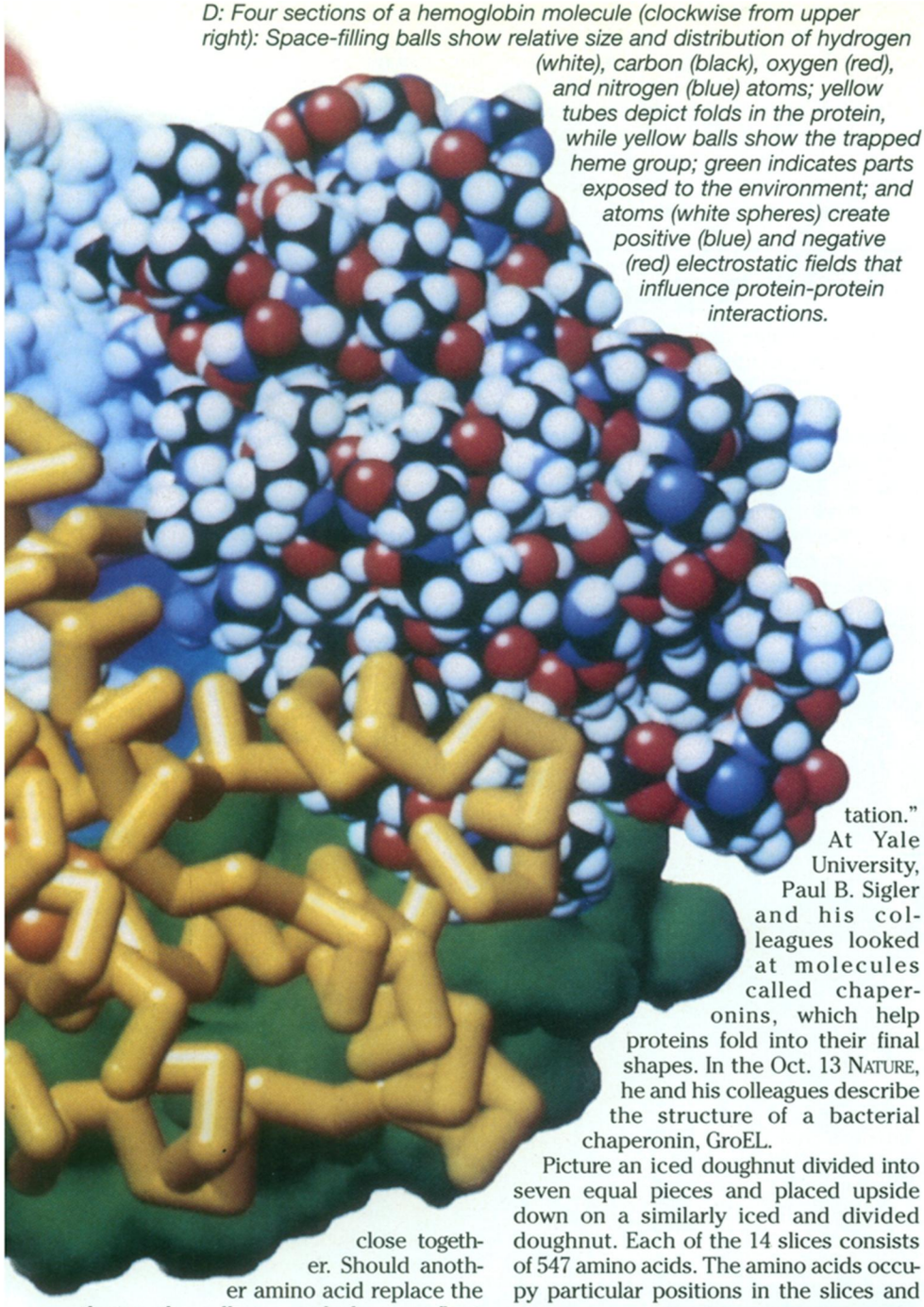
Already, an explosion in visualization techniques has revolutionized the depiction and analysis of molecules.

Jordi Bella *et al.*/SCIENCE

B: Ribbons show the spirals in collagen's three strands.

But computer graphics experts and their scientist-collaborators have not stopped there. They are also portraying, in ever clearer detail, cell membranes and the development of chick embryos. They are even attempting to make picture-perfect ultrasound images of the human fetus (see sidebar).

Recently, Berman and her colleagues captured on screen the structure of collagen, the one major protein motif left for X-ray crystallographers to decipher. Collagen is a protein in bone and connective tissue that forms from three parallel chains of amino acids that twist counterclockwise into spirals. Those spirals extend down a common axis, they report in the Oct. 7 SCIENCE. The spirals hold together because of a repetitive sequence: Every third amino acid is glycine, which allows the strands to lie

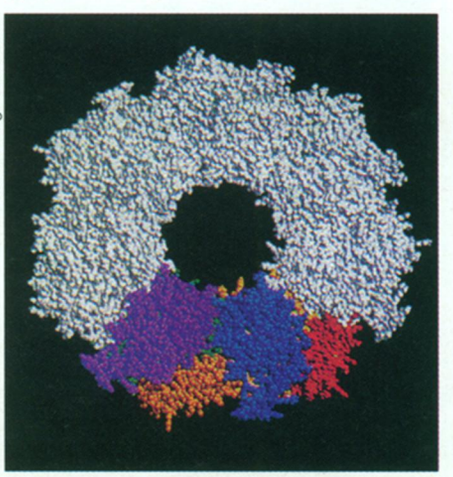


D: Four sections of a hemoglobin molecule (clockwise from upper right): Space-filling balls show relative size and distribution of hydrogen (white), carbon (black), oxygen (red), and nitrogen (blue) atoms; yellow tubes depict folds in the protein, while yellow balls show the trapped heme group; green indicates parts exposed to the environment; and atoms (white spheres) create positive (blue) and negative (red) electrostatic fields that influence protein-protein interactions.

tation." At Yale University, Paul B. Sigler and his colleagues looked at molecules called chaperonins, which help proteins fold into their final shapes. In the Oct. 13 NATURE, he and his colleagues describe the structure of a bacterial chaperonin, GroEL.

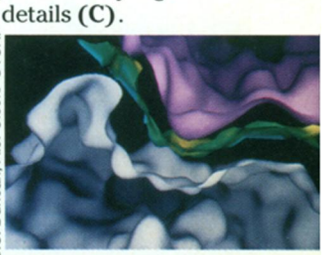
Picture an iced doughnut divided into seven equal pieces and placed upside down on a similarly iced and divided doughnut. Each of the 14 slices consists of 547 amino acids. The amino acids occupy particular positions in the slices and arrange into three layered sections, or domains. The innermost, icing domains link the doughnuts. Pieces of the middle domains reach across and touch adjacent slices, while the outermost domains form the opening of this central cavity.

Even this description fails to tell the whole story. Imagine now that some hungry youngster had decided to taste each of the 14 bits of doughnut and left a finger hole through the center of each. These portals extend deep into the slice and probably provide the chaperonin with a place for processing energy-transfer molecules called ATP, Sigler notes. Not all the graphics generated by Sigler's group show all these details **(C)**.



Kerstin Braig *et al.*/ NATURE

C: GroEL viewed from above with some domains colored.



B.S. Duncan, A.J. Olson/ ©TSRI

E: A close-up shows that some parts of two protein (white, magenta) surfaces are nearer (yellow) than others (green).

Based on these structural data, Yale colleague Arthur L. Horwich made specific changes in the amino acids of the GroEL central cavity. The modified GroEL could no longer hold onto proteins, indicating that GroEL corralled proteins in its core, Horwich reported, also in the Oct. 13 NATURE.

close together. Should another amino acid replace the glycine, the collagen might become flexible or unstable and cause disease, Berman says.

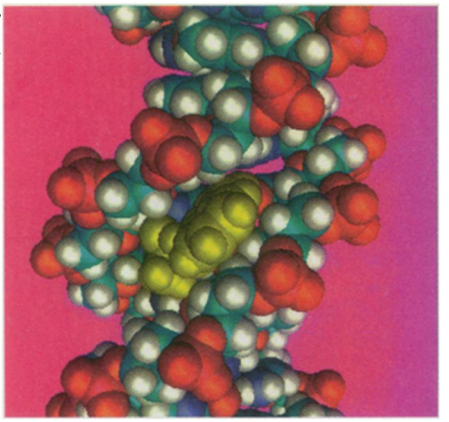
Interestingly, a single switch between a glycine and an alanine made crystallization, the first step in this kind of analysis, possible, Berman notes. To obtain a crystal, her group made and dissolved protein fragments that were 30 amino acids long, each with collagen's repetitive sequence — and each with this one switch. The substitution leads to a slight unraveling, noticeable in an image with amino acids shown as little bubbles **(A)**. When the fragments are portrayed as ribbons **(B)**, the substitution site becomes less evident, but the spiraling of the three chains into a triple helix becomes much clearer, she points out. "You see different things depending on the type of represen-

Like Sigler and Berman, Olson was schooled as an X-ray crystallographer. Early in his career, he wanted to know the structure of the proteins that surround the genetic material in viruses. Based on the first batch of data he and his colleagues collected, he built a model out of brass parts. However, that model proved useless in his quest to understand how the proteins self-assembled to make the viral coat. "That's when I realized that we really needed more flexible tools," Olson recalls.

Now, Olson spends as much time developing computer software — his "flexible tools" — as analyzing molecular interactions. His programs enable him to "see" a molecule in any number of ways **(D)**. "They don't look like anything from the traditional view, because molecules are smaller than the wavelength of [visible] light," Olson explains. "But visualization is a way of taking that structure and representing it in an interpretable way for the questions you are seeking answers to."

He can look at the bonds between atoms or ask the computer to draw a space-filling version, whose soap-bubble appearance indicates the volume taken up by the various molecular components. He can highlight the backbone of a protein to get a clearer view of how it folds. Or the computer can pinpoint surfaces exposed to the outside environment or delineate the distribution of electrical charges.

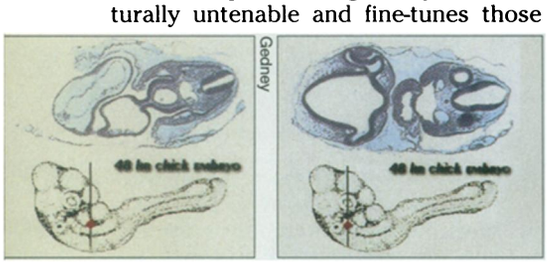
S. Broyde, B. Hingerty, Colvin/Sandia, DOE Office of Scientific Computing



F: Carcinogen (yellow) binding to DNA.

Those images help Olson and others take the next step — determining how one molecule links to another (see cover). They are also refining software that tackles the docking of one protein with another **(E)**. This second program represents the surfaces of proteins at greater and greater resolutions as it searches for and finds the regions where proteins can bind together, Olson explains. With each iteration, the program rules out connections that prove energetically or structurally untenable and fine-tunes those

Gedney



G: Two views of chick embryos; lines show locations of the cross section portrayed.

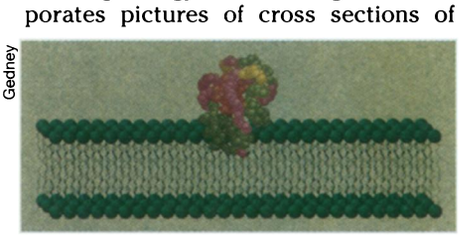
that seem likely, eventually homing in on the optimal orientations.

At Sandia, Colvin, too, investigates molecular connections. For one project, he portrayed a carcinogen attacking DNA **(F)**. "The DNA has grooves, and the carcinogen just drops down into these grooves like a key into a slot," he says.

Students, too, are reaping the benefits of these representations of the invisible world. At Purdue University in West Lafayette, Ind., Clark D. Gedney and his colleagues have developed several visualization procedures for teaching biology. One teaching tool incorporates pictures of cross sections of chick embryos taken at different stages of development **(G)**. Gedney's team added colors to highlight the various tissues and had the computer reconstruct the whole embryo. Rather than wield scalpels or fuss with mounting and viewing microscope slides, students click a computer mouse to see embryos at 13 stages of development. They can look at it whole or in cross section, notes Gedney.

Finally, another simulation enables both teachers and students to build their own cell membranes and then examine the effect of adding or removing an electron from the membrane **(H)**. The computer program makes sure the membrane works just as a real one does, Gedney says. □

Gedney



H: Visualization of a cell membrane with an incoming electron (red).

Reflections of clinical reality

It has become one of the rituals of pregnancy. A pulse of high-frequency sound (ultrasound) emanates from a device placed on a pregnant woman's bare abdomen. The sound waves travel into her body, echoing from various organs and tissues. Eventually, the waves return to the device, where they are detected. A computer quickly assembles the data — the strengths of the returning echoes — into a fuzzy black-and-white image on a video monitor.

For the mother-to-be, this first glimpse of her child can be both exhilarating and disappointing. She can see the new life that exists within her body, but the details are lost in the image's bleak haziness.

Sakas *et al.*

A pair of three-dimensional Images reconstructed from ultrasound data acquired in the 25th week of pregnancy (left) can be compared with a photo of the baby 24 hours after birth (right).

It generally takes an experienced clinician to make sense of the light and dark splotches — to point out the head, arms, and other fetal features — visible in the image. Even practiced physicians can have trouble interpreting ultrasound scans, whether used to check the development of a fetus or to assist in brain surgery or in the diagnosis of heart ailments.

To get more informative images out of ultrasound echoes, specialists in the visualization of data have been investigating the possibility of generating realistic, three-dimensional images from sequences of ultrasound scans. Such reconstructions are difficult, given the numerous factors — the noise — that can distort or obscure the data. The need for speed in the clinical setting adds to the challenge.

In one recent effort, Georgios Sakas and his coworkers at the Fraunhofer Institute for Computer Graphics in Darmstadt, Germany, used a workstation computer to generate high-quality three-dimensional images of a fetus in only a few seconds.

To do these reconstructions, the researchers wrote a computer program to clean up and visualize the fetal ultrasound data. The software digitally filtered out various types of noise, helped isolate relevant features and removed artifacts and extraneous material, and added shadows and shading.

Computer scientists Andrei State, Henry Fuchs, and their colleagues at the University of North Carolina at Chapel Hill have a more ambitious goal in mind. They want a clinician to see a three-dimensional image of a fetus — reconstructed on the fly from ultrasound data — not on a nearby screen but superimposed on the patient's abdomen.

Wearing special headgear that tracks head movements and displays the fetal image, a physician could examine a fetus as if he or she were looking directly at it in the patient's abdomen (see illustration). In this "augmented reality" system, any movement of the head would produce a corresponding change in the fetal image.

At present, a number of technological obstacles stand in the way of implementing such a scheme. Tracking equipment is still too imprecise, and computers can't generate the three-dimensional images fast enough.

UNC

View (bottom) of a reconstructed, three-dimensional fetal image (top left) superimposed on a pregnant woman's abdomen (top right).

Ultimately, the real test of any system for three-dimensional ultrasound imaging will occur in the clinic. Physicians will use the equipment only if it operates quickly, conveniently, and accurately — and only if they feel confident they can trust the results.

Sakas and State described their projects at the Visualization '94 conference held last month in Fairfax, Va.

— I. Peterson