Protein Images Update Natural History

A combination of improved biological techniques, hardware, and software has unleashed a flood of brightly colored images of protein structure. They're changing the way biology is done

When Max Perutz and his colleagues built the first atomic model of hemoglobin in the 1960s, it took up 16 square feet of floor space at the Medical Research Council's laboratories in Cambridge, United Kingdom. The structure rose from a plywood base in a forest of supporting steel rods to which were clamped brass wire and sockets and plastic-coated cable in red and white. It took a considerable act of visual imagination to ignore the thicketlike scaffold of rods and see the atomic architecture within. Completing that model was a monumental task, begun in 1937 with Perutz's arrival in Cambridge, and it stands as a monument to the way things will never be again in the burgeoning field of structural biology.

The arduousness of that decades-long saga—making crystals, interpreting x-ray diffraction patterns, solving the phase problem, and creating a structure out of those data—still sounds fresh in Perutz's voice, as this elder statesman of protein crystallography recalled the events in a recent conversation not long after he celebrated his 80th birthday. "First of all, you had the computer output of numbers giving the density distribution of the hemoglobin molecule in three dimensions. Then you had contour maps of the electron density drawn by hand, transferred onto plexiglass, and stacked up, like microtome sections through tissue. Then I had to measure the coordinates of peaks on these sections. *Then* I'd build a three-dimensional model."

Imaging is one of the most vibrant areas of science. Disciplines from astronomy to immunology are being energized by new imaging techniques, coupled with computer methods for manipulating images. In recognition of these advances, a seminar on Fundamental Issues of Imaging Science will be held in Atlanta on February 16–17, in conjunction with the AAAS annual meeting, AMSIE '95. To raise the curtain on this seminar, *Science* commissioned an article by science writer Stephen S. Hall on one of the most rapidly advancing subfields of imaging science: protein structures.

"Now," Perutz says, "with three-dimensional visualization on the computer, you can generate a contour map on the computer screen with a graphics program and can fit a three-dimensional model on this map. The whole process that took me 3 months can be done in 1 or 2 days. And the fantastic thing is that you can generate the structure of any protein. There are so many. ... It's an embarrassment of riches."

By any number of criteria—the proliferation of structures appearing on the covers of major journals, the appearance of new journals such as *Protein Science*, *Nature Structural Biology*, and *Structure*, or the exponentially expanding gallery of structures piling up in the Protein Data Bank at Brookhaven National Laboratory—this is a field enjoying a remarkable transformation. And the most visible manifestation of this exponential growth is an expanding oeuvre of breathtakingly intimate views of important biological molecules. In few fields does visualization play so central a role, not only because data are routinely converted into a succession of ever more precise maps and images, but because these images lead inevitably, and often instantly, to significant biological insights.

"You get the image, and you say, 'Aha, so *that's* how it works,' " says Wayne A. Hen-

Now Even Weaklings Can Image Proteins!

It began in the mid-1970s, in a crystallography laboratory at the Max Planck Institute in Martinsried, Germany. Many computer wires snaked around the floor, leading from the primitive Vector General graphics terminal to the main Siemens computer, and researchers in Robert Huber's renowned crystallography lab took to differentiating the wires (and the programs with which they were associated) by giving them names from the J. R. R. Tolkien classic *Lord of the Rings*. The program T. Alwyn Jones worked on, a bit of software designed to create three-dimensional atomic models of molecules from electron-density data, was dubbed "FRODO." "I think FRODO was actually called Sauron at first," says Jones, referring to the lord of the evil kingdom in Tolkien's trilogy, "because it was always bombing out."

Computer software has revolutionized visualization in x-ray crystallography, and FRODO was in the vanguard of that revolution. Many observers would agree with Harvard University biologist Don Wiley when he refers to the Welsh crystallographer as "*the* visual guru" of the field. "Alwyn Jones gets nowhere near the level of recognition he deserves," Wiley said. "Although many people have made significant contributions, he personally revolutionized how protein structures are handled as objects. There used to be fixed, wire models in every lab, and now no one builds physical models in the lab. What do my students spend all their time doing? They spend all their time in front of molecular graphics machines, and that's all because of Alwyn Jones."

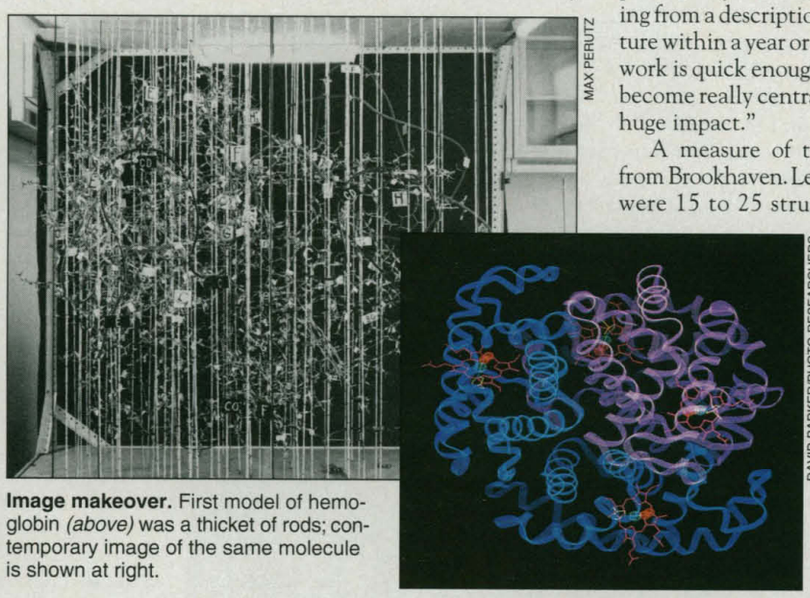
Jones, now at the University of Uppsala in Sweden, is hardly the only graphics whiz in the field. Indeed, in their quest for speed, accuracy, and informatively pretty pictures, crystallographers have a program for every atomic occasion—and a digital DaVinci for every program. There is XPLOR, developed by Axel Brunger at Yale University, which aims at producing more accurate models from crystallographic data. There is MOLSCRIPT, developed by Per Kraulis, a former student of Jones's now at Pharmacia, to create stereodiagrams and other views. There is GRASP, recently developed by Anthony Nicholls of Columbia University, which among other things depicts the electrostatic potential of a protein. And there is RIBBONS, originally worked out by Jane and David Richardson at Duke University and later developed by Mike Carson at the University of Alabama, to show a protein as sheets of domains.

Depending on the task, one can also select from MIDAS, RAVE, IN-SITE, DENZO, SETOR, SKEWPLANES, HEAVY, MEQLOT, SQUASH, and several commercially available programs, including QUANTA and PROLSQ. In addition, the Richardsons have developed the innovative educational program KINEMAGE, which allows students studying structural biology

drickson of Columbia University. The Hendrickson group's latest "aha" moment revealed how the intracellular, tyrosine kinase portion of the insulin receptor keeps its active site plugged to prevent phosphorylation until it receives the correct extracellular signal—an important step in hormone signaling from the cell surface to the nucleus. "First of all, you get a rush because you realize that you are the first human being to see how something looks. But I must say, the 'great aha' seems to be the case almost every time. This is not a case of making scientific progress by developing a hypothesis and then designing experiments to test the hypothesis. Instead, you're just going in and saying, 'What does this look like?' "

Don Wiley of Harvard University has a slightly different take on the power of the new images; he thinks they offer a jumping-off point for new hypotheses. "Actually, the human brain may be much better at dealing with visual information than with 15 steps of logical reasoning," he says. "I think visual information is very evocative, very rich to our minds. And when we get a good visual demonstration of what is going on with a molecule, we can mine it and ask a lot of new questions and use it as a solid framework for asking those questions. That's why structure is so powerful in so many ways."

Although x-ray crystallography has been around since early in this century, proteins are such complex molecules that unraveling their structure has been an extraordinarily slow and painstaking process. Perutz recalls that by 1970 only 11 structures had been solved since the birth of the field in the 1930s. (Another researcher says even that figure "sounds high.") But recent advances in molecular biology and protein crystallization, along with improvements in hardware and software, have merged to vastly increase the pace at which new structures of complex biological molecules are piling up. "In the early days, it was so difficult that when you got a structure done, much of the interest in the molecule may have already passed," says Hendrickson. "Now you are going from a description of activity to the structure within a year or so. Now crystallographic work is quick enough and so incisive that it's become really central. Timeliness is having a huge impact."



MAX PERUTZ

DAVID PARKER/PHOTO RESEARCHERS

Image makeover. First model of hemoglobin *(above)* was a thicket of rods; contemporary image of the same molecule is shown at right.

A measure of this acceleration comes from Brookhaven. Less than a decade ago there were 15 to 25 structures a year deposited in the Protein Data Bank. That rate underwent "an abrupt transition" beginning in about 1987, according to Joel L. Sussman, a structural biologist at the Weizmann Institute of Science who took over as head of the repository in January 1994. Currently, new structures are being registered at a rate of about 100 per month. If current trends continue, the data bank will swell to 30,000 structures by 2000.

Long, winding road

The current explosion of biologically intriguing molecular structures is the culmination of a long, winding road that began in Cambridge, United Kingdom, in 1913 when Lawrence Bragg solved the first structure of a

to view and rotate common molecules. The software is available on floppies, CD-ROM, or through the Internet, and complements the standard text in the field, *Introduction to Protein Structure*, by Carl-Ivar Brändén and John Tooze.

All these programs are, in a sense, the children of FRODO. "The history of FRODO is so complicated that you would need a genealogical tree, like the kings and queens of England," Jones said in an interview from Uppsala. "The impetus for creating it was that model-building was done using wire, and electron-density maps were done on sheets of plastic, and you ended up with something that looked like a gigantic Meccano-kit, an Erector set. And these were not easy to build—you had to be strong just to bend the wire. Computer graphics," he adds slyly, "meant that the weaklings could actually do the work as well."

In fact, of course, it meant far more. When crystallographers revise their structures by adjusting a bond angle or changing the distance between a pair of atoms, even the subtlest change usually requires small but critical fine-tuning in all other bonds—between thousands of atoms. Making these adjustments manually on the wire models could take months, if not years. With FRODO and its descendants, all adjustments are made simultaneously and automatically; indeed, in real time on the computer screen these adjustments literally ripple through a protein structure like a seismic wave.

Jones had a working model of FRODO by about 1978, and it was eventually adapted for use on an Evans and Sutherland graphics system, at that time considered the Cadillac of crystallographic workstations. Soon hundreds of crystallographers throughout the world were using FRODO to solve protein structures. Jones, meanwhile, got "fed up" with the program—and the responsibility of distributing updated versions, freely to academic researchers, at a charge to industrial labs—and decided to start again from scratch. "So now we have a new, more minimalist program—and 500 damn users again!" he grumbles affectionately.

The new program is "O," developed with Morten Kjelgaard at Århus University in Denmark. It is minimalist in the sense that it reduces the "fiddling capabilities," according to Jones, and includes a powerful database of known structures for protein domains that may be similar—or identical—to a short protein segment researchers are trying to solve. "The reason we all use 'O'," says Stephen Harrison of Harvard, "is because Alwyn incorporated into it elements that come out of insights into the nature of protein structure that he himself had and in fact was involved in developing." "There are no Nobel prizes for 'O' and 'FRODO,' " says another prominent x-ray crystallographer, "but they made a *huge* difference."

And what does the mysterious title "O" stand for? "That's a secret," Jones said. "I don't tell anyone, and only one person has guessed so far. But 'O' is not the end of FRODO."

–S.H.

Industrial-Strength Protein Structures

The revolution in x-ray crystallography has led biologists to see not only the atomic structure of molecules, but to envision the potential for immense profits in the area of "structure-based drug design." As Joshua Boger, the founder of Vertex Pharmaceuticals, told business writers at a press conference in 1990 (as recounted in Barry Werth's behind-the-scenes tale *The Billion-Dollar Molecule*), "You need to see every atom" in order to atomically tailor new drugs. "We're in control of the process," Boger predicted. "It's an information-based process, not a random process. It means we can get drugs faster to market and that they'll be better drugs."

So far, it hasn't worked out that way. "There is no doubt now," one prominent crystallographer remarked recently, "that the concept that just looking at a structure would be enough to design a new drug is wrong."

Few new drugs have reached the clinic by way of this high-tech approach, mostly because of obstacles long familiar to the pharmaceutical industry: solubility, efficacy, toxicity, and bioavailability (the ability of the molecule to get to the place where it will do what it's designed to do). "People give these talks about structure-based design, saying medicinal chemistry is old hat and once we know the structure, we'll be able to make five to six structures, and bingo, we'll have a drug," says Paula Fitzgerald of the Merck Research Laboratories in Rahway, New Jersey. "And it just doesn't work that way. ... Structure has certainly had a role in this company, but it's by no means only structure-based design. Medicinal chemistry continues to play a major role."

T. HYNES AND A.M. DE VOS

Twofer. Molecule of human growth hormone *(red)* bound to two receptor molecules *(blue and green)*.

The disappointing performance to date, however, obscures another reality: The structural lab has become a permanent and prominent feature of the pharmaceutical industry, not only as the core technology at start-ups like Vertex, but as an integral part of the process at older biotech companies such as Genentech and at long-established giants such as Hoffman-LaRoche and Merck. "Our program is drenched in structure," says Merck's Fitzgerald. There are now an estimated 50 to 60 structure labs in industrial settings, all dedicated to turning out new structures in weeks or months rather than years.

Not so long ago, however, techniques for solving the structure of biological molecules were so slow that structure labs had a tough time justifying their existence. Two companies that tried to overcome the obstacles were Wellcome in the United Kingdom and the now-defunct biotech company Genex, both of which maintained structure groups in the late 1970s. And both structure labs suffered the fate of those ahead of their time: They were phased out.

In the 1980s, however, a proliferation of technical advances began to change the picture. "I've been here at Genentech since 1983," said Anthony A. Kossiakoff, whose group has done basic studies on the interaction between human growth hormone and its receptor, "and I think we were among the first structure groups in biotech. But in the last 10 years, all the major companies have put together structural groups of reasonable size, so there's a real critical mass of crystallography done in industrial places."

Even if that critical mass hasn't yet paid off in dramatic new drugs, it has made two signal contributions. First, structural information can eliminate a lot of blind alleys in drug research. "If it takes you a year or two to do a structure, it's too late," said Merck's Fitzgerald, "but if you get it early, it really broadens your approach and stimulates your thinking."

Second, even industrial labs are turning out first-rate basic research. Kossiakoff, with his colleagues Bart de Vos and Mark Ultsch, has provided one striking example, in the area of ligand-receptor interactions. By studying co-crystals of human growth hormone bound to its receptor, the team showed that, in order to send a signal to the cell nucleus, a single molecule of HGH must bind with not just one receptor molecule but two, bringing the two receptor molecules together to form a dimer. "We had no idea, you see, what this interaction was like," said Max Perutz in praise of this solution. "It actually binds two receptor molecules together, and it's their combination that leads to sending a signal to the nucleus. And that was quite unexpected."

Not all aspects of the growth of industrial x-ray crystallography have been so salutary. Indeed, some researchers have raised concerns—particularly with regard to the free flow of information about structures that have commercial potential. Although the National Institutes of Health adopted a policy several years ago requiring any lab receiving NIH funds for its structure studies to deposit the coordinates in the Protein Data Bank, labs receiving funding from companies may place the coordinates "on hold" for a year, meaning the information is off-limits. At the end of 1994, approximately 180 structures deposited in Brookhaven were on hold, about 10% of the annual deposits.

In spite of such concerns, structure labs in industrial settings are here to stay. The rapid availability of accurate structural information means, says Kossiakoff, that "we're not driving without steering wheels, as it were." And having once driven with a steering wheel, no driver is likely to give it up.

–S.H.

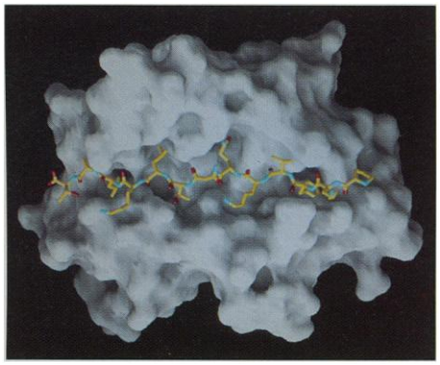
crystal. Building on previous work, Bragg realized that if a beam of x-rays was directed at a crystal, the x-rays would jostle electrons in the resident atoms of the crystal, causing them to oscillate and in turn generate a secondary shower of x-rays in every direction. Most of these waves would cancel each other out, Bragg deduced, but a few would produce distinct diffraction patterns on a film placed at a fixed distance behind the crystal. By interpreting that diffraction pattern, the investigator could begin to map areas of electron density in three dimensions, and from there infer—with a mix of intuition, trial-and-error tinkering, and a knowledge of the constraints of physical chemistry—a plausible three-dimensional arrangement of the atoms obscured by those electron clouds.

That worked fine for simpler crystals. But biological molecules, proteins in particular, upped the ante in complexity. It was not until 1934 that J. D. Bernal and Dorothy Crowfoot (later Hodgkin), at the Cavendish laboratory at Cambridge, demonstrated that protein crystals, handled gently and kept moist in their mother liquor, could yield x-ray diffraction patterns. Yet it would take decades to overcome the obstacles that remained between that initial insight and accurate three-dimensional protein structures.

The hunt for protein structures has never (until recently) been the field of choice for researchers hungry to score fast-break baskets. Just a few years ago, structural biology was a tiny fraternity, noteworthy more for evangelical zeal and sectlike devotion than

for productivity. The joke used to be that Sisyphus was their patron saint, delayed gratification the group ethic. Indeed, as recently as 1980, molecular structures were not displayed as images but as elaborate, hand-built contraptions that took up as much space as a small refrigerator.

Today, all that has changed. And as is often the case, the great burst of work that has become apparent in the last 2 or 3 years in reality derives from several new technologies that coalesced over more than a decade. The first transforming technology, all in the field agree, is cloning: The use of recombinant DNA techniques has allowed crystallographers to select a specific protein of interest, clone its gene, and make large amounts of relatively pure protein, which is necessary (although not, alas, sufficient) for getting good crystals. "We can express and purify biochemical quantities for any protein, or for that matter any nucleic acid, that we're interested in," says Stephen C. Harrison of Harvard University. "That means that instead of tackling just paradigm problems, as all of us had to do before the mid-80s, we can tackle *any* problem that we think is important enough to put the effort into. And that's totally different from our mindset a decade ago, when you took what nature gave you."



PARTHO GOSH

"Aha!" moment. The first images of the major histocompatibility complex bound to antigen proved revelatory to immunologists.

The second crucial technology is the one for coaxing crystals to form. Although that is still a black art, commercial kits are now available that allow many chemical conditions of crystal formation to be screened rapidly—"and many times," Hendrickson says, "this actually works." In addition, "brighter," more powerful sources of synchrotron radiation—100 to 1000 times more intense than at-home laboratory x-ray machines—have allowed more precise measurements of smaller crystals, and the evolution of automated, digital field detectors, which record tens of thousands of diffraction reflections instantly in computers, have rendered those blurry, enigmatic diffraction patterns captured on film a thing of the past.

Last but not least, extremely powerful software programs, most designed by crystallographers and distributed freely to the community, have immensely accelerated both model-building from the raw data and the graphic display of the solution. "What it does," says T. Alwyn Jones of the University of Uppsala in Sweden, who developed a pioneering program called FRODO and its successor, "O," "is reduce the turnaround time needed for refining a protein structure. You could build wire models, even today. But using a graphics system means you can get rid of errors and get better models, and then you can get on to seeing the biology in the model." (See box on page 620.)

Tools in hand

Outfitted with these powerful tools, structural biologists have become a bit like itinerant artists wandering the biological countryside. They tend not to be, strictly speaking, virologists or immunologists or cell or molecular biologists; instead, they travel to noteworthy trouble spots or prominent vistas in those scientific provinces, returning with pictures that often have an enormous impact on fields where they are little more than visitors.

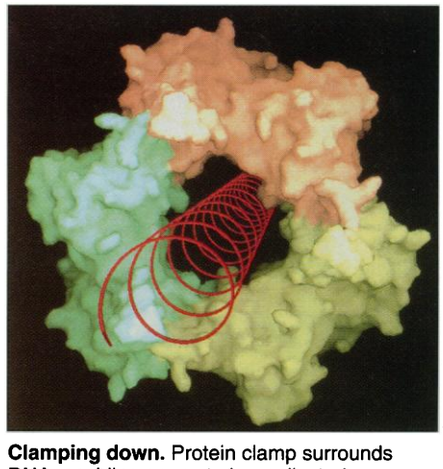
Take DNA replication. In May 1992, a team led by John Kuriyan of Rockefeller University solved the three-dimensional structure of a prokaryotic protein known as a DNA clamp. In bacteria, this doughnut-shaped protein slides along DNA "like a curtain ring on a curtain rod," according to Kuriyan. Once the clamp is slipped onto DNA, it provides a moving platform for DNA polymerase (the enzyme that replicates DNA), preventing the polymerase from falling off the double helix while it does its job. The structure of this bacterial protein revealed that the clamp is a highly symmetrical assembly of two monomer subunits, each composed of three structural domains of identical topology, although showing striking dissimilarity in DNA sequence.

In eukaryotes, however, the protein that carries out the analogous function—known as processivity factor PCNA—was only two-thirds the size of the bacterial protein, and it had no conspicuous similarity to it in amino acid sequence. In an article last December in *Cell*, Kuriyan and co-workers—Talluru S. R. Krishna, Xiang-Peng Kong, and Sonja Gary at Rockefeller and Peter M. Burgers at Washington University School of Medicine—published the structure of a DNA clamp from the yeast *Saccharomyces cerevisiae*, and that image reveals what biochemical data could not. The eukaryotic clamp has a different design: Three molecules, each composed of two identical topological domains, combine to form a ring structure. But the wonder of the different design is that, in spite of the wide disparity in DNA sequence, the structure is almost identical topologically to the earlier published structure for the bacterial clamp. "This is a particular case," said Kuriyan, "where visualization led directly to an idea of function and how evolution used that structure."

But of the "aha" moments provided by protein structures that have immediate impact, perhaps the quintessential example is the three-dimensional structure of the class I major histocompatibility (MHC) molecule. When it first appeared in *Nature* in 1987, Oxford immunologists Alain Townsend and Andrew McMichael predicted that "every immunologist's pulse will race" in response to the first glimpse of the binding site where antigen is presented to the immune system. The Harvard team that solved the structure—led by Pamela J. Bjorkland (now at the California Institute of Technology), Jack L. Strominger, Don Wiley, and their colleagues—provided an image that addressed a prominent question: How many binding sites did the molecule possess? The answer was as clear as the single, deep, well-defined groove in the structure.

The structure also illustrated a crucial advantage of structural studies. "Crystal structure analysis really provides two things, the second much more often than the first," says Wiley. "First, occasionally, you look at a structure and you get a lot of information right away, and the classic example of that is the structure of DNA. Much more commonly ... structure provides a solid framework within which to pursue future science and interpret past science. You are able to design much more incisive experiments, able to do experiments in a more focused manner."

In an elegant series of just such well-focused experiments, the Harvard group and others have used the initial image of the MHC molecule to dissect antigen presentation in spectacular detail. Each MHC subtype possesses a universal berth at each end of the groove, which forms hydrogen bonds with the terminal amino and carboxylate groups common to all peptides. Different subtypes, however, possess slight variations in the dimen-



CELL, VOL. 79, 30 DECEMBER 1994

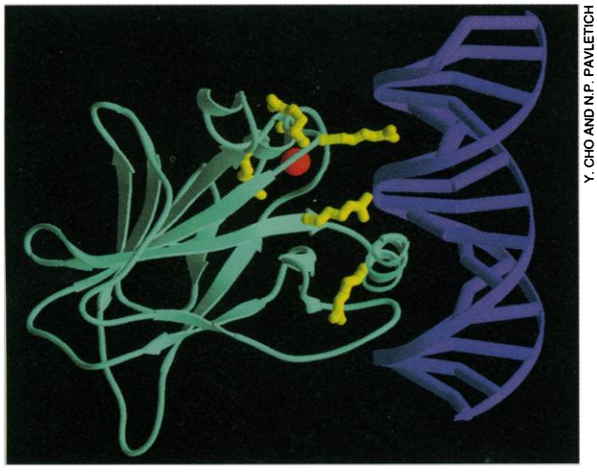
Clamping down. Protein clamp surrounds DNA, enabling genes to be replicated.

sions of the groove itself, accommodating the variety of side chains that distinguish various peptides. Once the peptide—now known to be eight to 10 amino acids in length—is locked in this groove, the complex makes its way to the cell surface, where the MHC holds up the peptide in a kinked conformation, many of its side chains exposed to T cells, whose receptors in turn distinguish differences down to a single amino acid.

Sometimes a new and striking image has as much sociological as scientific impact. Again, take the case of the MHC molecule. Wiley argues that a number of immunologists had a very good intellectual picture of MHC processing prior to 1987. And yet the structure, when visualized, confirmed these intellectual advances and made them explicit to an entire field, providing a rallying point and a point of departure for future experimentation.

Hendrickson remembers going to an immunology meeting not long after the MHC structure appeared where, he says, "there wasn't a single talk that didn't show that image. That molecule focused thinking in immunology just tremendously; it became clear that the mode of recognition suggested by this structure solved the problem of how so few molecules could account for the great specificity conferred. Realizing that the peptide lies in the groove allowed one to appreciate how the immune system does this part of its job."

Sociology aside, perhaps the most obvious advantage of visualization is the degree to which the operational sites of molecules can be pinpointed—and pinpointing those sites opens the way to practical interventions. One example of protein-DNA interaction that is of keen interest because of its therapeutic potential is the binding of the *p53* tumor suppressor gene product to DNA.



Y. CHO AND N.P. PAVLETICH

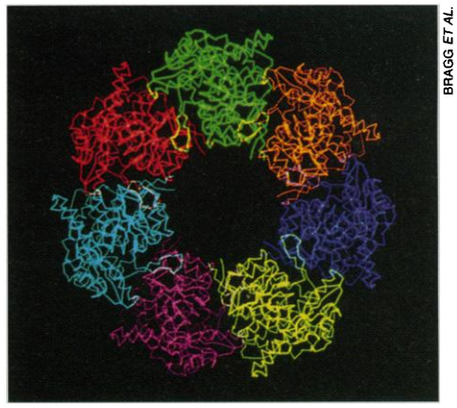
Ties that bind. Image of p53 protein binding to DNA may have great therapeutic potential.

In the last several years, the p53 protein has emerged as the most frequently mutated gene in human tumors, and it is believed to play a critical role in responding to damage to DNA. "p53 in the cell appears to respond to events that may lead to this unregulated growth that is characteristic of the tumor state—mutations, other kinds of damage to DNA, chromosomal rearrangements, and genomic instability in general," explains Nikola P. Pavletich of the Memorial Sloan-Kettering Cancer Center, whose group published the structure in the summer of 1994. The researchers focused on a core domain of the p53 protein, a segment about 200 amino acids long, where the majority of inactivating mutations seemed to appear. By the time they had finished plotting the location of the complex's 6000 atoms, they had identified six sites where mutations appear to cripple DNA binding.

In the published structure, these mutation hotspots appear in bright yellow. "If you pick your colors appropriately," says Pavletich, "you can instantly see that most of the mutations occur at the DNA binding surface of the p53 protein." The hotspots highlight two different routes to biological breakdown. A pair of the most common mutations is seen in locations on the protein that normally come into direct contact with the DNA; mutations here cause the protein to lose critical DNA contacts, and that is apparently enough to disrupt DNA binding.

The four other common mutations also affect the DNA binding surface of the protein, but not directly. These mutations involve small structural changes in the scaffolding of the protein that may either cause shifts of amino acids or destabilize the overall structure of the protein so that it no longer interacts with DNA. The ultimate goal of this work is to address what Pavletich calls "a very big question out there," namely, "can you do anything to restore the function of this mutated gene in cancer patients? *p53* is the closest we've come to finding a common denominator [in cancers], and thus presents a very attractive target for therapy."

If improvements in hardware and software have made it possible to produce images of protein structures at remarkable speed, another innovation is just as important in how those images get used: the Internet. Once the atomic coordinates are deposited in the Protein Data Bank at Brookhaven, the structure becomes available electronically to any researcher in the world—through the World Wide Web, for example. Researchers can call up a structure, view it on their workstations, tinker with the image, and turn it almost as if it were in their hands (a CD-ROM version of the data bank, updated every 3 months, puts this capability even within reach of PC and Mac users). "We're averaging one network access every minute of every day, 60,000 a month," says David R. Stampf of Brookhaven, "and a year ago, none of this even existed."



BRAGG *ET AL.*

Gro-th factor. Image of Gro-EL, a chaperonin, a type of molecule that mediates ATP-dependent folding of proteins.

It is a testament to how far x-ray crystallography has traveled in recent years from its Sisyphean origins that one of its most respected practitioners suggests that this most arduous and exacting precinct of biology may be suffering from a "glitz problem." The downside of all the computer graphics power, says Yale University's Paul B. Sigler, "is that people tend to get carried away with the beauty of these structures and forget about the chemistry." With "ribbons glimmering in the sunlight," he says, "people tend to leave out the science."

Many crystallographers privately acknowledge that prettiness unadorned with the nuts and bolts of biochemistry can be a form of visual pollution in a field built on the unyielding rigor of bond angles and protein folds. "The field of x-ray crystallography is an interesting intersection of physics, chemistry, and biology," says Kuriyan, "and perhaps from that point of view, aesthetics are irrelevant, or even distracting."

"But I think the aesthetics of display are very important in communicating information," he continues. "I think the analogy to natural history in the 19th century is really striking. There is the analogy of artists going into the Brazilian rain forest and coming out with illustrations of these fantastic new species. It's not an accident that on the *Beagle*, an artist was brought along to record what they saw. It's not an accident that we remember Audubon's drawings of birds. This," he added, motioning toward the luminous, multihued plumage of a DNA clamp, "this is natural history, 1994."

–Stephen S. Hall

Stephen S. Hall is the author of Mapping the Next Millennium: The Discovery of New Geographies, *a survey of imaging across scientific disciplines.*