Biology Goes to the Movies

New video technology enables neuroscientists and cell biologists to see dramatic processes that could only be inferred before. Now come quandaries about how to publish movies

GASPS RIPPLE THROUGH THE RAPT AUDIENCE as it recognizes the figures on the screen—creatures familiar in name and form, though rarely seen in action. As the characters rush forward, some suddenly stop as though they have struck an invisible barrier. Their progress thwarted, they distort and spread out, like faces pressed against a window. After a while, they reach back with grasping arms, searching for an anchor to help pull themselves away. Once they succeed, they're off in a new direction.

If you want to see this suspense thriller don't waste time looking in the movie listings or the sci-fi section of your local video mart. Check your university seminar schedule instead. That's because these characters aren't Hollywood creations, but the tips of extensions put out by embryonic nerve cells, making the journey from a mouse's retina to its brain. The film, by Pierre Godement of the Université Pierre et Marie Curie in Paris, and Carol Mason of Columbia University is just one of the new biology classics that have been playing to packed houses—as Godement and Mason's did at the recent neuroscience meeting in St. Louis.

Over the past decade, advances in video technology and digital image processing have provided new and sophisticated tools for spying on living cells and recording their behavior on videotape. Video is a natural choice for studying movement, and researchers are now using it on many different levels. They study movements within cells, such as the flow of ions across membranes, or the trafficking of molecules or organelles. And they watch the wanderings of cells themselves, during both embryonic development and adult life.

The resulting videos are not only rich in biological information but visually captivating as well, and scientists with videos to show are in demand on the seminar circuit. But the surge of interest in scientific videos presents a challenge to traditional channels of publication. In some cases, videos are central to the understanding of a piece of research, but there is currently no vehicle for publishing video material. However, at least one journal, ***Cell Motility and the Cytoskeleton***, has taken a step to bridge this publishing gap with a planned annual video supplement. As demand grows, others are likely to follow its lead, establishing videos as an acceptable—and citable—means of collecting and presenting data.

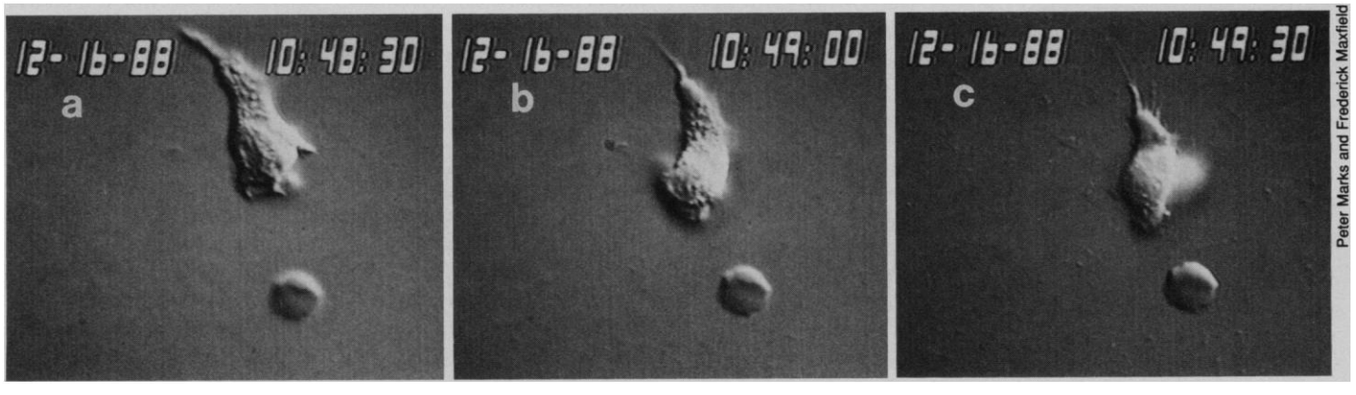
Videos are a welcome addition to the biologist's tools, says neurobiologist Larry Katz of Rockefeller University. "People have been speculating about processes, based on static images," he says, "but you don't really know what's happening in real time until you can see the process take place before your eyes." New video technology lets researchers do just that. "The key words are better resolution, better contrast, better magnification, and cheaper," says Nina Allen of Wake Forest University, who worked with her late husband, Robert Allen of Dartmouth, and Shinya Inoue of the Woods Hole Marine Biological Laboratory to lay the groundwork for the current video revolution.

Astronomers had been using highly light-sensitive video cameras for years before biologists jumped on the bandwagon. In 1980 the Allens got the idea from Nina's father, an astronomer, to couple such a device to their microscope. The video camera enabled them to enhance the image, bringing out features normally invisible through a light microscope. Within a few years, the Allens, Inoue, and others had their video systems linked to computers that could digitally process the video images. This vastly increased the power of the process by further reducing background noise and enhancing specific features of the image.

Even before the power of digital processing was fully realized, the Allens were using their analog video set-up to watch microtubules. These fibers, which make up the cell's internal skeleton, are only 25 angstroms in diameter, too small to see with a normal light microscope. In the video camera, the microtubules seemed to act like a railroad switching system, shuttling the tiny packets of neurotransmitters and other organelles around the cell.

The Allens, in collaboration with Raymond Lasek of Case Western Reserve University, as well as a separate Woods Hole-based team headed by Thomas Reese of the National Institute of Neurological Disease and Stroke, went on to show that purified microtubules could shuttle organelles bidirectionally, in vitro, provided they were supplied with a mixture of cell proteins. That mix seemed to contain a protein "motor" that not only caused organelles to move along the microtubules, but would also link purified microtubules to a glass surface and propel them along the surface like snakes.

The Reese group began searching for the



Peter Marks and Frederick Maxfield

motor protein, using video imaging as its assay. They added various fractions of cell extract to purified microtubules and watched to see if the microtubules snaked along a glass surface; movement would indicate that the fraction they were testing contained the motor. Eventually, they purified a protein that drives transport along the microtubules and named it kinesin. "From A to Z, the work was dependent on the video assay," Reese says.

In the kinesin studies, the videos were made under bright visible light. Researchers have also made use of fluorescent dyes to bring other cellular processes into view through the video camera. For example, with calcium-sensitive fluorescent dyes developed by Roger Tsien of the University of California, San Diego, researchers can follow split-second changes in the distribution of calcium, an important cellular signaling molecule. In another approach, fluorescent tags are attached to biological molecules, and video is used to track their movements within the cell. And with membrane-binding fluorescent dyes, biologists can label cells and follow them as they grow through a sea of unlabeled cells.

It was this last use of fluorescence—in dyes that bind to membranes—that enabled Godement and Mason to make their striking time-lapse film of extensions of retinal neurons en route to the brain. Fluorescent labeling of cells is not new, Mason says, but it used to be impossible to label and observe living cells, because fluorescence levels bright enough to see would cause deadly damage. Highly sensitive video cameras have changed all that, allowing filming of the cells at very low levels of fluorescence.

The resulting videos give researchers a new perspective on events they could previously only deduce from still images of dead tissue. Mason and Godement's video, as well as a similar one made by David Sretavan with Larry Katz and Torsten Weisel at Rockefeller University, shows the growth cones, as the growing tips of nerve cells are called, apparently contacting several types of cells, and picking up at least two types of signals—one that stops their forward progress and another that coaxes them in a new direction. Such insights come out of watching the growth cones in motion, Mason says: "[The moving image] suggests what you should be looking for experimentally."

That is perhaps the most valuable feature of movies as data: Actually seeing a process provides a gut feeling about how it might work. "This stuff is very phenomenological," says Katz. "It's like studying animal behavior. If you know a behavior, you can start asking questions to take the behavior apart." Rockefeller University's Amiram Grinvald, who makes movies of neuronal activity in cat and monkey visual cortex, agrees: "The brain is an extremely good machine to do visual processing. Once you see a movie, and you see how things change, you can analyze the information with your brain in a way that's not easily done any other way."

Indeed, videos can be so enthralling that some researchers worry that they may eclipse the scientific information contained in the images. Mary Hatten of Columbia University studies the migration of neurons from mouse brains along fibers made from support cells called radial glia. She worries that audiences may be seduced by her movie of cultured neurons gliding along like trains on a monorail and forget that the video is not an end in itself, but merely an assay to ask questions about the proteins that guide the neurons. "I get a little touchy about it when everybody says, 'Come and show us your video,' " she says.

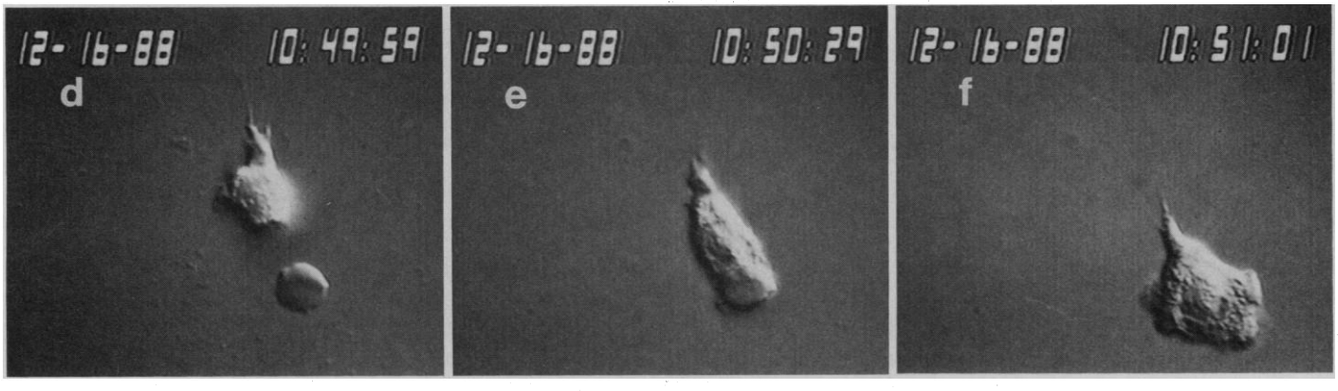
Like Hatten, Ronald Vale of the University of California, San Francisco, who was on the NIH team that discovered kinesin, says he now uses videos as a routine assay, and that makes it unnecessary to show a video when presenting his work. "The microtubule-movement-on-glass assay is standard," he says. "Everyone accepts it, so you don't even need to publish a figure from the video. You can just publish the velocities or whatever parameter you are measuring."

But for other researchers the video is not merely an assay—it contains vital information that is not easily expressed in other ways, such as images of the correlated activity pattern of hundreds of neurons. And that brings up a problem: If a video is really crucial to a piece of research, how can the information it contains be made part of a publication? "You can't do justice to the video with anything you can print on a page," says Stephen Smith who works on imaging processing technology at Stanford University. While it may be possible to make your main point with still photos from the video, he says, subtle points are bound to be lost, and the results are always disappointing.

Fred Maxfield of Columbia University tried his own solution to the video publishing quandary. Maxfield, who uses calcium-sensitive dyes to study the effect of calcium on the movements of neutrophils (phagocytic scavenger cells of the immune system), recently published a pair of papers containing still images from a video. In each paper was a footnote in which Maxfield offered to mail the video to anyone who sent $10 to cover costs. "I made 100 copies," he says, "but only two people sent requests."

Maxfield says his effort may have been too offbeat to draw much of a response. But it does point out another problem: Because his video was neither peer reviewed with his paper nor formally published, it would be of limited use to his colleagues, who could cite it in their own papers only as a personal communication.

That problem might be eased if there were a way to publish a video along with a paper, as part of the data supporting the paper's conclusions. Until recently there was no such publishing vehicle, but that is about to change. The journal *Anatomical Review*, which is undergoing reorganization, is con-



Nouvelle vague. *In a series of video-enhanced differential contrast images made by Peter Marks and Frederick Maxfield of Columbia University at intervals of 30 seconds, a white blood cell called a neutrophil migrates toward and engulfs a specially treated erythrocyte.*

sidering publishing videos, and *Cell Motility and the Cytoskeleton* intends to begin publishing its annual video supplements next month.

Founded in 1980 by Robert Allen, *Cell Motility* had video publishing as a goal right from the beginning. But its first effort, in 1983, failed. There was almost no demand for the videos, partly because the journal chose video discs as a format, and at the time few researchers had access to video-disc players.

Now under the editorship of Bill Brinkley of the University of Alabama, Birmingham, the journal is trying again—this time with videotapes. They have high expectations that the more accessible format and the greater number of researchers who are now using video will make the venture a success. The first videotape supplement, a kind of "Greatest Hits of Cell-Biology Research Videos," will be out in December, and Brian Crawford, executive editor at Wiley-Liss, the journal's publisher, says he has been deluged with calls from subscribers eager to get the tape. Subsequent supplements will contain video data submitted and peer reviewed as part of papers published that year in the journal.

But some researchers question whether mailing out videotapes or discs is really the best way to publish video data. Their proposed solution: fully electronic journals, through which one could receive, at a computer work station, both the printed text and figures from a paper, and an accompanying video. Video information can be transmitted over current research networks, says Daniel Masys, of the National Library of Medicine, although the recipient must have the software to convert the digital information back into video. But within a year or so, Masys says, networks such as Internet will be able to transmit a processed video image to anyone with a monitor able to display it. Intriguing as this idea sounds, publishers aren't rushing to start electronic video journals, says Patricia Morgan, director of publications at the American Association for the Advancement of Science. The demand, she says, is not high enough to make such a venture worthwhile.

Once journals like *Cell Motility* break the ice, however, that demand may grow, as an ever increasing contingent of video researchers becomes less willing to settle for publishing static images. And, in the end, video may not only change the way research is done in many areas of biology, but also how results are disseminated. "Our first tape is a way of showing what the medium has to offer," says Crawford, of Wiley-Liss. After that, there may be no turning back.

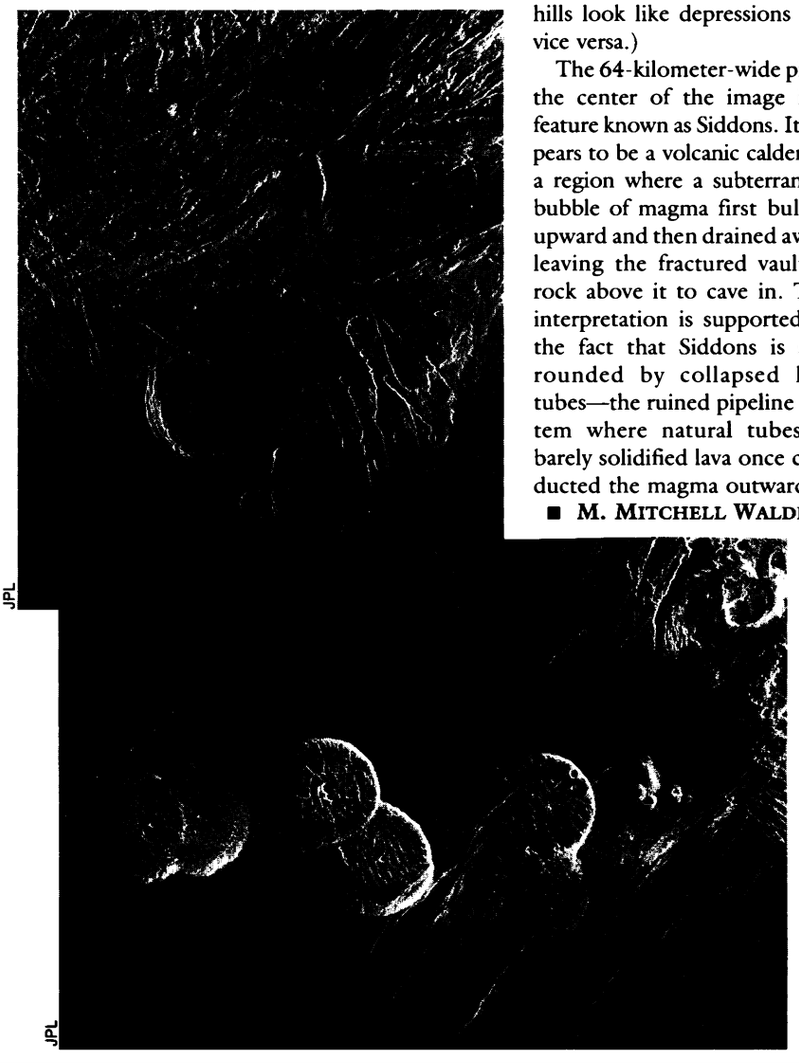
■ MARCIA BARINAGA

New Maps of a Very Strange Place

Almost everywhere the Magellan spacecraft looks on the hot, cloud-wrapped surface of Venus, it is finding symptoms of rampant volcanic activity. Take the two images shown below—among its latest radar snapshots of Earth's sister planet.

Looking like the mold on some long-forgotten leftovers, seven domed hills (bottom image) march across the eastern flank of a highland known as Alpha Regio, in the southern hemisphere of Venus. The domes are volcanic features averaging 25 kilometers in diameter and 750 meters in height, say Magellan scientists. One theory is that they were produced by thick, viscous lava that oozed up through vents in the ground and then flowed out radially across the surrounding plains like so many giant mudpies. Alternatively, they may be bulges where the surface rocks have been pushed upward by magma welling underneath.

In the side image, a high-resolution mosaic of several Magellan radar scans shows a 341-kilometer-wide panorama of Lakshmi Planum, a high plateau that stretches across roughly the same northern latitudes that Alaska occupies on Earth. Rising some 3.5 kilometers from the surrounding plains, Lakshmi is thought to be a tectonic uplift similar to the Himalayas and the Tibetan plateau, which were produced by the collision of India with Asia. Lakshmi is about the size of Africa and tends to have very steep sides. Shown here is a close-up of the southern edge, where the dark, smooth, lava-covered surface of the plateau suddenly falls off to the rough, broken terrain that rings its base. (Both images are shown here with south at the top; otherwise, the way Magellan's radar illuminates the Venusian surface would make hills look like depressions and vice versa.)



The 64-kilometer-wide pit in the center of the image is a feature known as Siddons. It appears to be a volcanic caldera—a region where a subterranean bubble of magma first bulged upward and then drained away, leaving the fractured vault of rock above it to cave in. This interpretation is supported by the fact that Siddons is surrounded by collapsed lava tubes—the ruined pipeline system where natural tubes of barely solidified lava once conducted the magma outward.

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