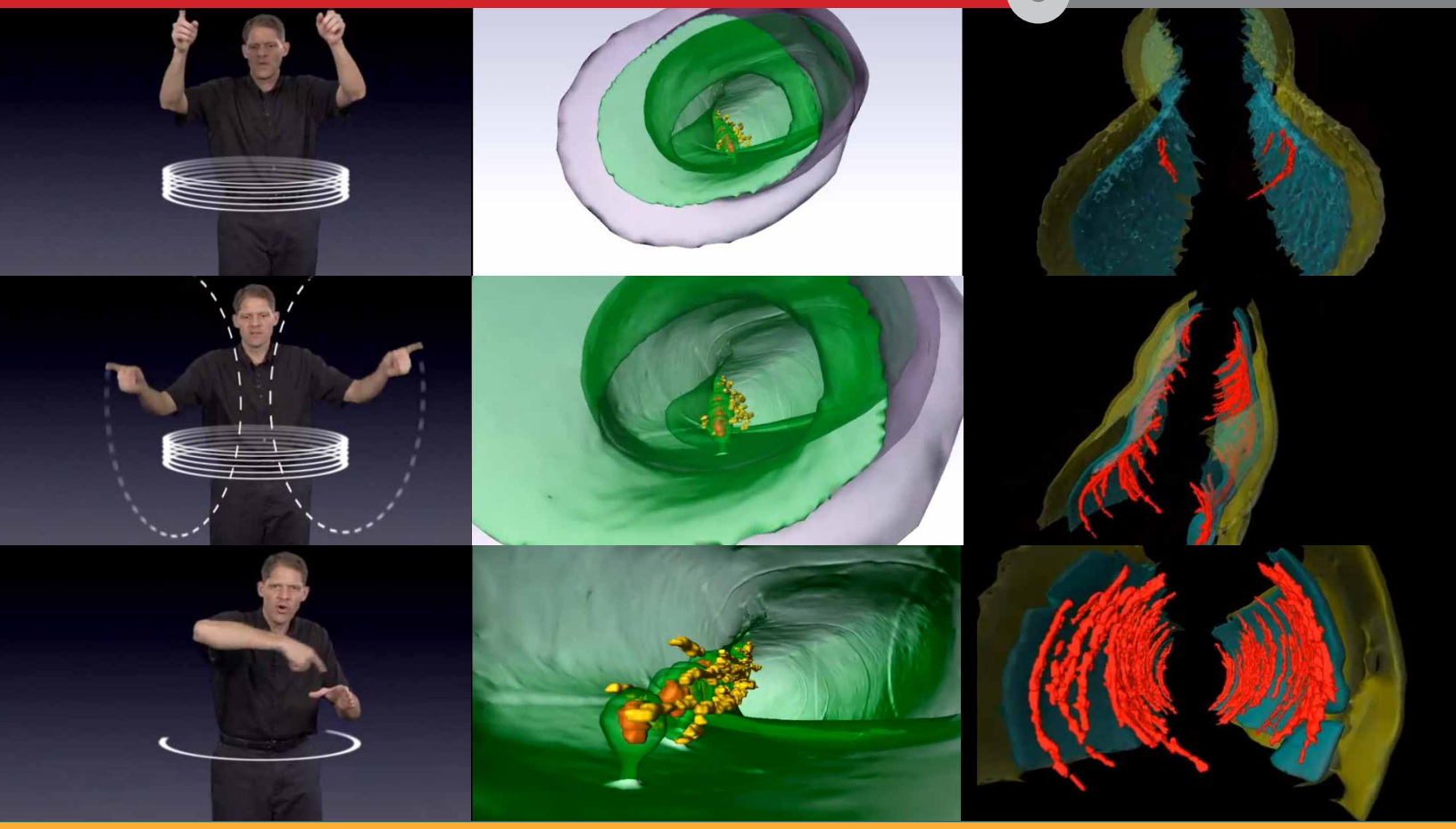
Viral Videos

(AND BACTERIAL ONES, TOO)

by Katie Neith



Grant Jensen is a high-powered movie producer. You won't see his name on any of this fall's Hollywood blockbusters, but in the field of cell biology, he has revolutionized the view that researchers, and even the curious public, get of the insides of cells. He does this through the innovative use of a digital camera and specialized electron microscope, which together enable a field called cryo-electron microscopy, or cryo-EM.

Now, he's taking what he's learned over the past 13 years using cryo-EM and sharing it through a series of online videos that serve as visual textbooks to teach to the world the skills and knowledge needed for cryo-EM studies.

"The nature of our work is very visual," says Jensen, a biologist who is one of just a handful of experts in this growing field, in which the electron imaging of cryogenic samples allows scientists to image biological specimens in as close to a natural, or native, state as possible.

By stringing together high-resolution microscope snapshots taken of such samples from various angles, Jensen and his team have been able to create three-dimensional moving pictures of cells, viruses, and bacteria. "My lab members and I have been really thrilled with the impact of the movie presentations we've put online with our papers," Jensen says.

Being able to image, in their native state, the macromolecules inside cells has provided the group with new information on the architecture of cell walls, on how cells determine their shapes, on how they move, on how they metabolize and store nutrients, and on how they fight each other.

"We've also discovered, just by seeing cells better than has ever been possible, entirely new structures in bacteria and viruses," Jensen says. "The images we've been able to produce have also revealed completely new ideas about the evolutionary relationships between different families of bacteria and bacterial secretion systems and phages. We've also used the microscope to study the structural biology of HIV. Excitingly, we've begun to understand structures inside the cell related to viral entry and egress."

Special Effects

It all started by taking a chance. As part of the Moore Foundation's 2001 gift to Caltech, the Institute's scientists were tasked with identifying potential projects for funding, especially those that might be considered "high risk, high reward."

"One of the things the faculty realized was that, in the future, we really ought to be doing cellular imaging by electron microscopy. So the administration took some of the Moore money and bought the world's best electron microscope at the time," says Jensen.

That great microscope was a state-of-the-art FEI Polara transmission electron microscope, and it helped Jensen decide to join Caltech's faculty in 2002.

The Polara uses an electron beam to illuminate samples that have been flash-frozen into a fixed state and kept below –150 degrees Celsius. This process eliminates much of the damage that can be done in traditional microscopy, for which samples must be fixed, embedded in plastic, sectioned, and stained. The process of freezing the samples instead captures cells in action, binding them in a layer of transparent ice.

"At the time that the microscope was purchased, and when all these people moved to Pasadena and aligned their lives with mine, no one knew what we would discover if we looked inside cells in this new way," Jensen says. "So it would have been totally impossible to fund the microscope through traditional pathways."

That's because nailing down funding for new research, especially when it employs expensive and unproven instrumentation, often involves a sort of chicken-or-egg problem, he says. If an institution decides it needs to do the kind of high-end cryo-EM that he's made such good use of, they need two things simultaneously: an expert and a microscope. If they don't have the microscope, it's hard for them to recruit an expert. And if they don't have an expert, they can't write the grants to get a microscope.

"The Moore Foundation trusted Caltech that they would use their money wisely, allowing the Institute to overcome this barrier—they solved the chicken-or-egg problem," says Jensen.

Early success using the microscope—such as revealing, for the first time, certain structures inside bacteria, and individual HIV-1 viruslike particles—then led to additional federal grants, an appointment for Jensen as a Howard Hughes Medical Institute investigator, and an ever-expanding team. Which is exactly what unrestricted funding is meant to do: seed research that can then garner funds and resources from more traditional sources.

"As we had continued success, some of people in the lab who were doing cutting-edge research decided to stay on with the team longer. Their expertise, experience, and abilities allowed me to expand the team even further because they were able to train and guide the new members," says Jensen. "After five or six years it became very clear that imaging cells with cryo-EM was opening dramatic new windows into the cell, and that attracted just the very best structural biology postdocs. The microscope was absolutely critical to their recruitment. It nucleated the whole effort."

Some of the people he's recruited along the way are computer scientists

and biologists who are also interested in graphics and visualization.

"Because of that, we've found ourselves both with 3-D data and people who were interested in trying to depict that data with computers in the most useful way possible," says Jensen.

The results can be seen on his lab's website, where you can witness a cholera-causing bacterium delivering a toxin to its competition; see the unique structures of a spirochete—a type of bacteria that is part of the termite's microbiota—and the way it moves through termite guts; and gain an inside view of HIV development.

"We've seen things that no one even knew existed, inspiring completely new directions of inquiry in bacterial cell biology," says Jensen.

A close-up of the Polara electron cryomicroscope that Jensen uses shows the front of the column, with the sample loading chamber on the left and the aperture controls on the right.

Required Viewing

Now Jensen is hoping to spread the knowledge he's gained through watching movies by making movies; in February 2015 he released free and publicly available video-recorded lectures on the uses of cryo-EM so that others can be empowered to make their own discoveries.

"There's been a big burst of interest from structural biologists and cell biologists who want to learn about cryo-EM," says Jensen. "I think my online course is going to help people around the world get started in the field on whatever day they decide they want to learn about it. The videos are particularly needed because we have a lot of people who want to learn the field, and a small number of people who can teach it. It's not like your average biochemistry class, where every college has a teacher."

In addition to offering a comprehensive online learning platform for professionals in the field, Jensen is using the video lectures in his classroom instruction as well. It's a pedagogical choice that has led to some surprising results. Earlier this year, for instance, he asked his students to watch the lectures at home and then come to class prepared to review certain study questions in front of their peers.

"While it was a little unusual at first for the students to be on the spot, the class became really talkative," says Jensen. "All of a sudden the whole class was very open and much more communicative. It completely broke the teacher-student barrier to have the students at the board."

The students weren't the only ones for whom the experience was disorienting and exciting.

"It turned out to be challenging for me because I no longer controlled everything that was going to be presented that day," he continues. "I think that made the students even more comfortable because now all of us were standing in front of the group exposing the boundaries of our knowledge. It democratized the classroom."

Jensen recognizes that the future of teaching in science and math will involve—and possibly revolve around—these kinds of recorded lectures. And in his field in particular, he believes online course instruction is a better tool than any textbook could be.

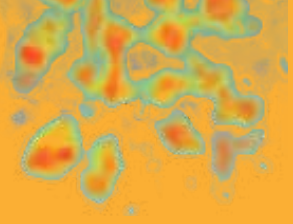
"Things can move in an online class," he explains. "I can build a diagram element by element, explaining each piece of it. That's very difficult to do in a textbook figure."

Given his track record of success in all things cryo-EM so far, it's probably fair to say Jensen and his online classes are moving in the right direction.

"The bet that people made in buying this microscope, and in coming to join my team, has paid off richly in ways that no one could have even anticipated," says Jensen. "In part because of the Moore investment, cryo-EM is having a growing global impact on many different levels. And we're just getting started." e&s

Grant Jensen is a professor of biophysics and biology at Caltech and an investigator with the Howard Hughes Medical Institute (HHMI). The National Institutes of Health, the Beckman Institute, HHMI, and the Gordon and Betty Moore Foundation help support his work in cryo-electron microscopy.

More information on Jensen's cryo-EM online lectures can be found at cryo-em-course.caltech.edu.



In 2002, when Grant Jensen arrived at Caltech, the Institute had **ONE** of only a few high-end cryo-electron microscopy facilities in the world.

Jensen has trained 20 postdocs in cryo-EM.

Jensen collaborates with some **40** microbiologists around the world to address key questions using cryo-EM.

His lab has published nearly **100** studies featuring results from the technology.

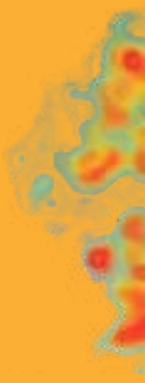
At Caltech alone, more than 27 faculty members now use the cryo-electron microscopy facility for a variety of research projects.

OVER **40** high-end cryo-EM labs are now established across the globe. FIVE are led by former postdocs of Jensen's who now have their own labs in Singapore, Switzerland, England, Canada, and the United States.

Funding agencies like NIH, NSF, and HHMI have now begun to allocate resources for cryo-EM. "Many institutions have chosen to invest large sums of money in microscopes like ours as people have seen what they can do," says Jensen.

48 instructional videos in cryo-EM are now available on numerous online platforms. Jensen's introductory video alone received more than 2,300 views in its first two months online.

Jensen says he's 100 percent sure he will continue to incorporate his online lectures into his classroom teaching.



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