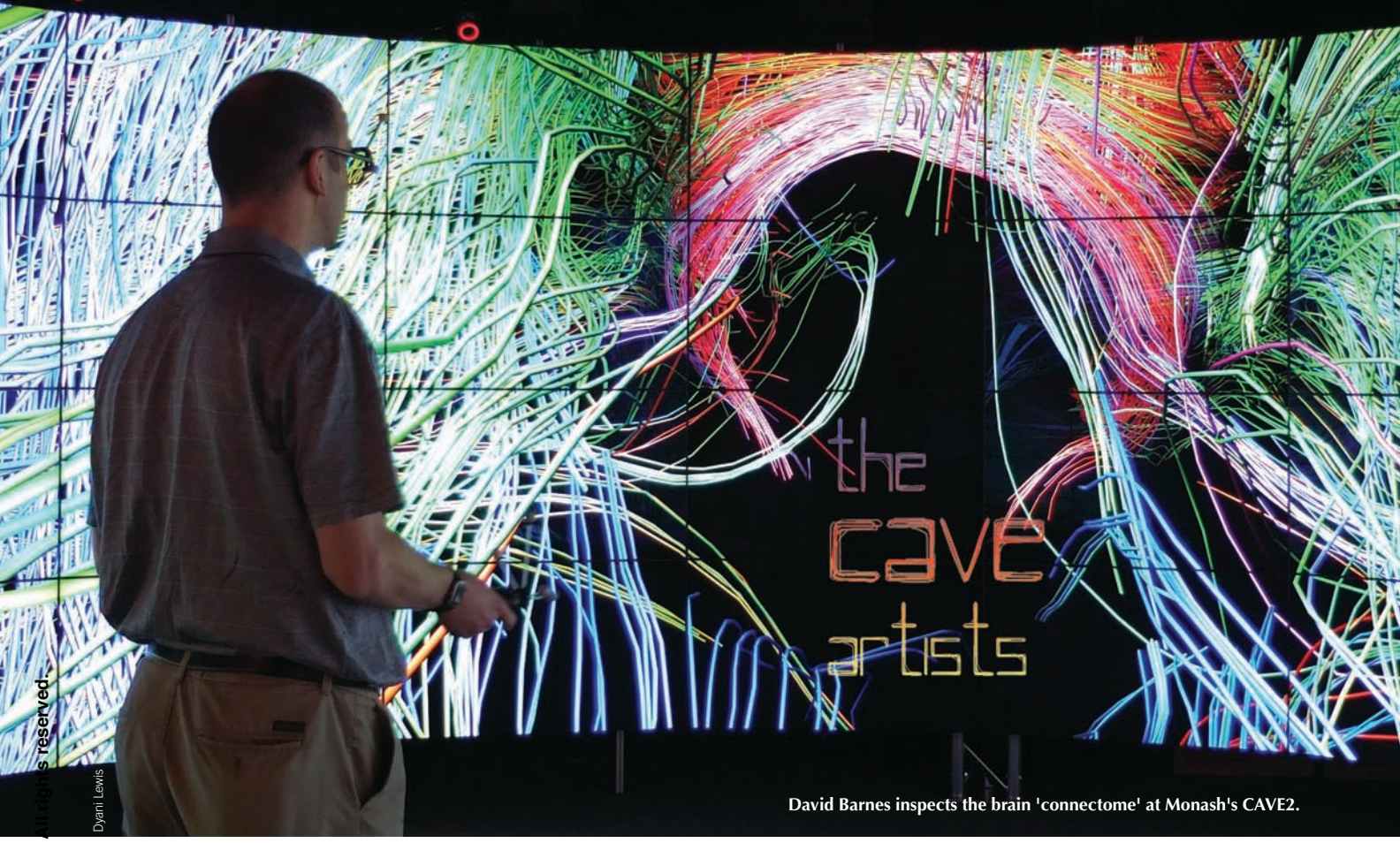



Dyani Lewis

David Barnes inspects the brain 'connectome' at Monash's CAVE2.



In the era of big data, biomedical databases are brimming with protein structures, image collections and genomic sequences. As the data mount, new 'cave automatic virtual environments', or CAVEs, are being built to help researchers pick through the files. **Dyani Lewis** meets the pioneers behind these large-scale visualization labs to see whether immersive virtual worlds can cut through the complexity.

Walking into the CAVE2 at Australia's Monash University in Melbourne, the first thing that strikes you is its immensity. What appears to be an enormous electronic billboard encircles the space, forming a cylindrical room with a 24-foot diameter. The images displayed on the 80 high-definition liquid-crystal display panels beam out at a crisp 84-megapixel resolution. And with a pair of stereo glasses, they pop out of the eight-foot-high display wall in three dimensions (3D).

In the virtual driver's seat is David Barnes, a radio astronomer by training who runs the new CAVE2 facility. He holds what looks like a chunky television remote controller with four lollipop-like baubles attached to the top. This wand, together with the similarly adorned 'reindeer glasses' and motion-tracking sensors, control navigation so that Barnes can fly across the surface of Mars, explore an Egyptian temple or examine pathways of neural activity.

CAVE2 is the state of the art in electronic engineering and computer visualization technologies—and Monash's CAVE2, which opened its doors late last year, is one of just two such facilities in the world. The first, slightly smaller CAVE2, with 72 panels instead of 80, started accepting scientists at the University of Illinois at Chicago (UIC) in October 2012. The circular CAVE2 design of both facilities is the latest immersive virtual environment to emerge from UIC's Electronic Visualization Laboratory (EVL).

Proponents of these 'cave automatic virtual environments' say they could be a boon for basic research scientists wanting to visualize complex 3D structures—from elaborate molecules to whole organs to networks of gene or protein interactions. CAVE2 "will push some science forward," Barnes says. "It's a matter of finding out the right way to apply it."

## Thinking inside the box

Olusola Ajilore is finding a way. A neuropsychiatrist at UIC, Ajilore is using the CAVE2 in Chicago to study whether impairments in white matter integrity underlie depression in the elderly. Within the immersive 3D lab, he can virtually step into and walk through the brains of his research participants, or at least their diffusion tensor images. "It looks really cool," says Ajilore—so cool, in fact, that across the world Barnes is using Ajilore's brain 'connectome' images to show off the potential of the newly minted CAVE2 in Melbourne.

Standing inside the connectome is like being in the middle of a large tangle of multicolored electrical cables. Long fingers of green project out from the display, blue cables fall like curtains to the side and a thick tangle of red hovers near the center. Zoom out and meaning starts to emerge from the chaos. The red is soon recognizable as the corpus callosum, the fleshy junction relaying information laterally between the brain's two hemispheres, and the green and blue cabling indicate front-back and top-bottom flows of neural activity. In an instant, the computer-generated colors have decoded and simplified the complicated highways of the mind.

In November, Ajilore presented his connectome work in a poster at the 2013 Society for Neuroscience conference in San Diego. Reactions ranged from "Is this art?" to "This should be a TED talk." But more important than its visual magnificence is what Ajilore hopes to detect in the connectome when he's in the CAVE2. "We might be able to appreciate more subtle differences that aren't detectable when you're looking at what is essentially three-dimensional data in two dimensions," he says.

The predecessor of the CAVE2s in Melbourne and Chicago was UIC's first CAVE, a square room, ten feet across, with graphics projected onto three walls and the floor. Built in 1991,

the original CAVE was named for its obvious grotto-like qualities, but also after Plato's Cave, the allegorical place where shadows become reality for those inside.

Since its inception, variations on this basic CAVE design have cropped up all over the place. There are CAVEs now in museums, architectural firms, car manufacturing companies, government laboratories and universities. Developers have also tinkered with the construction, creating cubic models that completely surround the user, as well as spherical and pentagonal enclosures. And as display technologies have improved, projector-based CAVEs have been joined by systems such as NexCAVE and CAVE2, made of high-definition, 3D-enabled panels (see 'Step into the CAVEs').

But as commonplace as CAVEs have become, the use of these multimillion-dollar visualization facilities as research tools has so far left scant trace in the biomedical record. Most reported applications of virtual reality environments in the life sciences literature focus on their use in medical training or as a virtual environment to encourage patient rehabilitation—not drug development, even though CAVEs are often touted for this research application.

As such, the question of whether scientists and their institutions have managed to turn infrastructure spending on CAVEs into biomedical advances—let alone whether newer CAVE designs are worth the investment today—is an open one. Monash's CAVE2, for example, had a price tag of A$2 million ($1.8 million), not taking into account construction costs to accommodate it or the operational costs to fund software development and personnel, which are often recouped through hiring fees in the hundreds of dollars per session.

## CAVE dwellers

Harel Weinstein is one scientist who sees value for money in CAVEs. In 2007, he and his colleagues at the Weill Cornell Medical College in New York were trying to nail down how the addictive drug cocaine interacts with its target, a protein that normally pumps the neurotransmitter dopamine out of the synaptic clefts between neurons for reuse. "We went into the CAVE"—the original square-room kind—"and we positioned the cocaine where our computation said it would sit," Weinstein recalls, "and then we said, 'What can we do to prove that it sits there and nowhere else?'"

When viewing a simulation of the subtle, yet dynamic, flexing and bending of the dopamine transporter, Weinstein and his team noticed that just above where cocaine bound sat two helical structures that waggled into close proximity to each other—a feature that had not been obvious from looking at the interactions on a two-dimensional desktop computer. Knowing this, the researchers devised a way to reversibly cross-link these two helices in an engineered version of the dopamine transporter. Using this molecular clamp to lock in or lock out cocaine molecules in tissue culture cells expressing the engineered protein, they showed that the cocaine bound to the transporter at precisely the place where the computer modeling had predicted[1].

> "With the CAVE, our eyes just see patterns."

Without identifying the helices in the CAVE, "this idea would never have come to us," says Weinstein. Importantly, the work also confirmed a suspicion that Weinstein had all along: that cocaine uses the same binding pocket on the transporter as dopamine. Efforts to find a drug therapy for cocaine addiction would now have to steer clear of simply looking for an inhibitor of cocaine binding, lest it also disrupt vital dopamine function. "That was a revelation."

Robbert Creton, a developmental biologist at Brown University in Providence, Rhode Island, had a similar 'aha' moment when he stepped into his institution's CAVE to look at confocal microscopy images of a developing zebrafish embryo. Creton was trying to determine whether a sac-like organ, known as a Kupffer's vesicle, which develops around 12 hours after fertilization, could be responsible for establishing left-right asymmetry in the growing fish embryo. Creton hypothesized, but hadn't been able to prove, that the mechanism could be related to the distribution of tiny hair-like cilia that project into the fluid-filled sac. On his computer monitor, the cilia on one surface of the vesicle had been hard to distinguish from those on the opposite surface, and quantifying differences in density between the two surfaces impossible.

"The moment that we stepped in the CAVE, it was pretty obvious," says Creton. What he saw in the CAVE, but had failed to see on a flat screen, was that the cilia were indeed unevenly distributed throughout the vesicle. This explained how they could control the flow of fluid to establish a left-right chemical gradient that affected zebrafish development[2].

**Step into the CAVEs:** Examples of cave automatic virtual environments from around the world.

| System | Configuration | Display type | Year first built | Notable examples |
|---|---|---|---|---|
| **Projector-based systems** | | | | |
| 'Classic' CAVE | Cubic room, ten feet across, image on three walls and floor | Minimum three rear-screen projectors for walls and one down projector for floor; 8–120 megapixels | 1991 | UIC; Brown University; Weill Cornell Medical College; numerous others |
| Mechdyne six-walled CAVEs | Cubic room, ten feet across, image on four walls, plus floor and ceiling | 24 rear projectors; 100–200 megapixels | 2007 | Cornea (King Abdullah University of Science and Technology; KAUST); C-6 (Iowa State University) |
| Allosphere | Aluminum sphere, 32-foot diameter, with walkway bridge through center | 26 projectors under bridge and at entrance | 2007 | University of California–Santa Barbara |
| StarCAVE | Pentagonal room, ten feet across with 11.5-foot ceiling, image on five segmented walls (top and bottom tilted inwards) plus floor | 15 rear projectors for walls and two down projectors for floor; ~68 megapixels | 2008 | Calit2 |
| **Panel-based systems** | | | | |
| NexCAVE | Scalable curved display, 5–7 columns of panels; top and bottom tilted inwards | 17–21 Xpol panels; ~30 megapixels | 2009 | Calit2 (17 panels); KAUST (21 panels) |
| CAVE2 | Circular room, 18–20 columns of four panels, wrapped around 320–330°; 24-foot diameter, eight feet high | 72–80 3D LCD panels; ~84 megapixels | 2012 | UIC (72 panels); Monash University (80 panels) |
| WAVE (Wide angle virtual environment) | Vertically curved wall; 5×7 panel display; 20 feet long, 12 feet high | 35 3D LCD panels; ~50 megapixels | 2013 | Calit2 |

In his current work, Weinstein is interrogating more complex molecular interactions, involving "a whole environment of machinery," including multiple proteins as well as the biological membranes they associate with. These systems, he says, are "even more difficult to fathom" without an appropriate visualization facility. By building 3D models of these complex molecular networks, Weinstein is able to ask questions and use 'what if' scenarios to direct wet lab investigations, as he did for the dopamine transporter. "We say, 'It looks like this thing is involved, so what if we mutate it, or what if we change it, or what if the membrane now is more rigid than it was before?'"

It's in these increasingly complex systems that advocates of CAVEs see their greatest value. Jürgen Schulze, a computer scientist who writes visualization software for CAVEs at the California Institute for Telecommunications and Information Technology (Calit2) in San Diego, says that when it comes to sifting through large data sets, computer algorithms and supercomputing facilities are often enlisted to do much of the heavy lifting. But large-format 3D displays put the onus back on the researchers' own visual acuity to explore the data and extract meaning.

"You can't just tell a computer, 'Find patterns,'" Schulze notes. "You have to tell it what kind of patterns you're looking for, and then you'll only find those patterns." With the CAVE, he says, "our eyes just see patterns. You don't have to make any effort to do that."

## Branching out

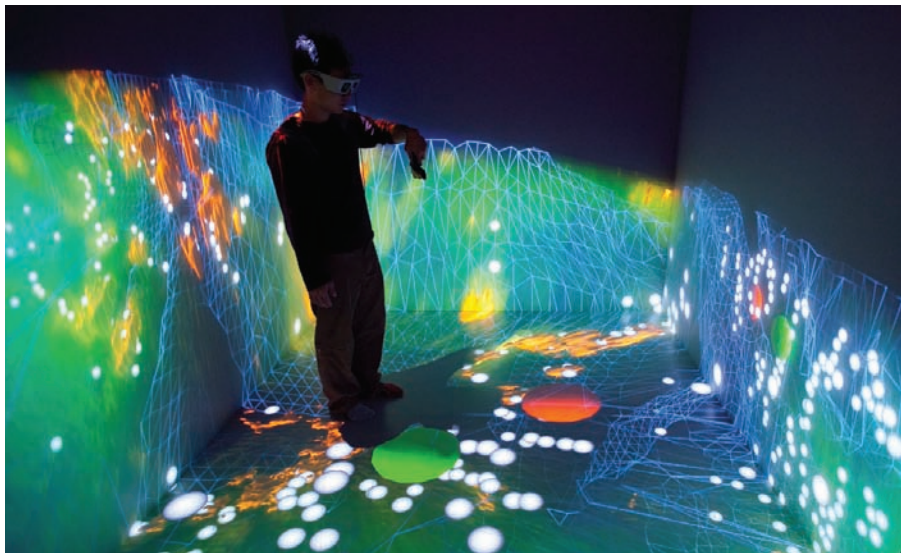
When the first CAVEs began appearing on university campuses, large-scale visualization was often the endpoint of research studies. Scientists would demonstrate structures to students and colleagues but rarely actively investigate those structures. Nowadays, visualization is designed to be part of the research process—with each viewing prompting new questions and ways to sort and combine data sets. "You get in this very rapid iteration process," says Larry Smarr, director of Calit2. "It's like climbing a tree. You don't just jump to the top of the tree. You go branch by branch. And you have to, at each branch, figure out where to go to next." With their spacious interiors that can accommodate more than a dozen viewers, the CAVEs also generate a collaborative experience, he says.

> "Innovative ways of being able visualize data will hopefully lead to better discoveries."

Not everyone, however, is convinced that CAVEs are changing research so dramatically. Philip Bourne is a computational biologist who used a CAVE "on and off" at his former institution, the University of California–San Diego. He found the immersive environment to be particularly useful when dealing with "very large and very complex" molecules, such as ribosomes. But he now sees CAVEs as being of most benefit in education, not research. "I couldn't point to a publication of ours and say, 'This piece of science was done because of the CAVE,'" says Bourne, who this month became the first associate director for data science at the US National Institutes of Health in Bethesda, Maryland.

Drew Berry, a biomedical animator at the Walter and Eliza Hall Institute of Medical Research in Melbourne, is another skeptic of CAVEs' value for research. For those who do need to really get inside their data, Berry's money is on head-mounted devices. Once virtual reality goggles come down in price, "you can essentially create a virtual CAVE for $300," he says.

Already today, there's a small desktop-sized visualization unit called FluidVis that's commercially available. A combination of a 70-inch 3D display, special glasses and proprietary software, FluidVis, from Fluidity Software of Somerville, Massachusetts, retails for around $25,000—a fraction of the cost of a full-sized CAVE—while still capturing "a lot of the immersive benefits," says Andrew Forsberg, a Fluidity cofounder and research scientist at Brown University's Visualization Research Lab. FluidVis also has an added benefit of accessibility, notes Creton, who has used the tool. "It's more convenient because it's right in the lab," he says.



Christie, Weill Cornell Medical College

**CAVEd in:** Virtual reality is helping researchers explore the neural activation patterns of zebrafish.

Competing—and cheaper—systems could be built with software developed by Zeynep Gümüş, a computational biologist at Weill Cornell. Gümüş had used her institution's CAVE to identify genes specifically involved in mouth cancer development[3] and to find regions of noncoding DNA that help drive cancer more generally[4]. After being approached at conferences by scientists who told her they would conduct similar network visualizations, but for the lack of a CAVE, Gümüş and her graduate student Vaja Liluashvili designed iCAVE—the interactome CAVE. According to Gümüş, this software works just as well in a CAVE as on a desktop system assembled from off-the-shelf components that generally cost less than $2,000.

Price and infrastructure hurdles aside, perhaps the biggest challenge for CAVE2s and other full-size visualization facilities is awareness—"people not knowing what is possible," as Andy Johnson, head of research at EVL, puts it. Johnson doesn't see this problem as insurmountable, though. "Once people see an example that's close enough to what they want to do, it starts to click and they start getting ideas," he says.

Scientists like Ajilore are only too happy to be leading the charge. "I think there's a huge upside in having new ways of visualizing large data sets," he says. "If we have innovative ways of being able to visualize that data and understand that data, hopefully that will lead to better discoveries."

*Dyani Lewis is a freelance science journalist based in Melbourne, Australia.*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