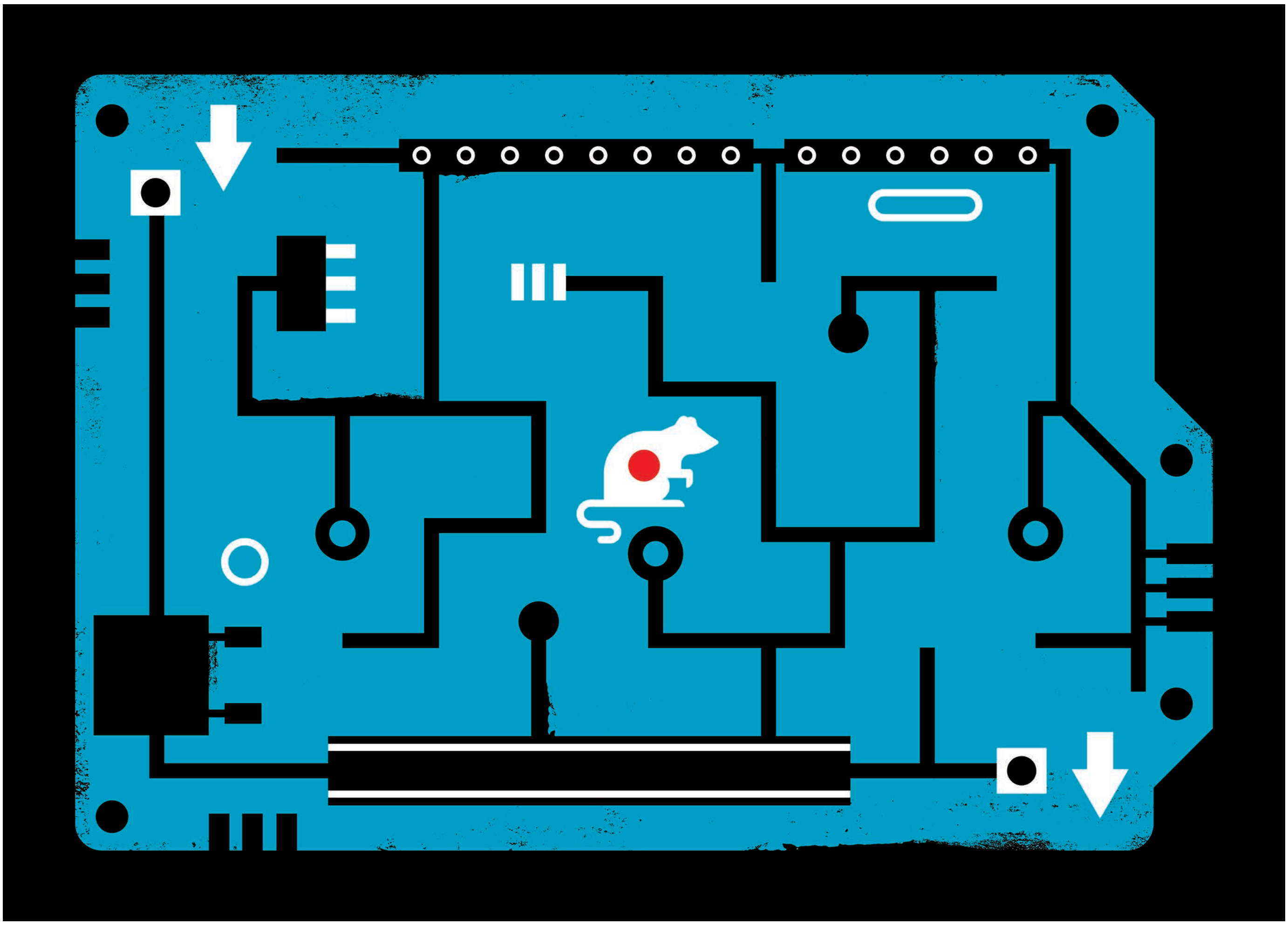
TOOLBOX

THE MAZES WITH MINDS OF THEIR OWN

Automated 'smart mazes' free behavioural researchers from the tedium of monitoring animals. They also boost data quality and reproducibility.

ILLUSTRATION BY THE PROJECT TWINS



BY CHARLES Q. CHOI

As a graduate student, behavioural neuroscientist Mark Brandon spent hours running rodents through a T maze, a test of learning in which animals run down a track and then turn either right or left. The task was useful, but boring. So, when he secured a faculty position at McGill University in Montreal, Canada, Brandon wanted to skip the monotony.

He acquired an automated T maze from MazeEngineers, a start-up firm in Cambridge, Massachusetts. Much more than a simple labyrinth, the maze has doors that rise from the floor after a rodent passes to stop it going backwards, and integrated video monitoring to document the animal's behaviour. Once the rodent has completed a task, the maze directs it back to the beginning. By analysing which neural circuits are active during these tests, Brandon and his colleagues hope to shed light on how the brain links memories with time. "The automated T maze has been incredibly helpful," he says.

Today, such systems are becoming increasingly common and sophisticated. "We're starting to see technologies that have made major advances elsewhere, like touchscreens and microcontrollers, make their way into behavioural-research labs," says Alexxai Kravitz, a neuroscientist at the US National Institute of Diabetes and Digestive and Kidney Diseases ▶

in Bethesda, Maryland. But despite the automation, the human touch is often still needed to ensure these gadgets work correctly.

Researchers use mazes to test an animal's mental traits, such as memory and attention. For much of the twentieth century, mazes forced rodents down elaborate paths, exploring mental limits. Today's set-ups are considerably less convoluted, says MazeEngineers founder Shuhan He, making the results easier to incorporate into statistical analyses. "Mazes to me are about decisions and outcomes — they allow key tests of cognition." But because researchers increasingly want to look at lots of animals in each experiment and to collect as many behavioural data as possible, automation has become a necessity.

Scientists first used video tracking to monitor rodent behaviour automatically in the 1990s, starting with computers that identified an animal's centre of mass to recognize simple behaviours, such as whether the rodent sought out or avoided a particular stimulus. Now, by tracking the head and other body parts, software can recognize subtler behaviours, such as sniffing, grooming and urinating. Tracking systems also exist for creatures such as fruit flies and zebrafish.

"Now you can just start a program and automatically track an animal in a maze, and get the data to analyse instantly after the animal is finished," says Justin Rhodes, a behavioural neuroscientist at the University of Illinois in Urbana–Champaign who studies the effects of exercise on the brain.

Automation also promises increased accuracy and objectivity by reducing the human role in experiments — for instance, when it comes to deciding whether an animal froze or merely paused. And it provides standardized equipment and tasks so that researchers can compare their results directly.

MazeEngineers' automated T mazes for mice start at US$4,900. Video-based mazes and software are also available from such companies as Clever Sys in Reston, Virginia, and Noldus in Wageningen, the Netherlands. Rhodes favours Clever Sys's HomeCageScan system (about $55,000 for four cages) for its ability to track multiple animals. That, he says, is not trivial, "given how they can climb over and under each other". Behavioural neuroscientist Evelin Cotella at the University of Cincinnati in Ohio prefers Noldus's EthoVision software ($5,850 per licence), for its user-friendly interface.

That's not to say that smart-maze systems work perfectly out of the box. Scientists often have to fiddle with settings including lighting and visual contrast to get video-tracking software to work, Rhodes says. And they must measure how accurate their systems are at recognizing behaviours. "It's not going to be perfect, but people aren't, either," Cotella says. "What software will be, compared to people, is consistent."

Cotella's team had to test how well its system categorized behaviour, compared with the researchers. The team also had to optimize parameters such as how many pixels per video frame had to remain unchanged to count as the mouse 'freezing'. It took about six months for the group to feel confident with the system, says Cotella. "We've now had it for a year, and we'll start publishing studies from it in the next month. It's definitely helped us move faster."

Another option, the IntelliCage from TSE Systems in Bad Homburg, Germany, tracks animal movement using subcutaneous radio-frequency identification (RFID) tags. "You don't have to worry about light like you do with video tracking; it runs even in total darkness," explains Daniela Oettler, a scientific associate at TSE.

IntelliCage fits inside any conventional lab cage. Each of its four corners houses devices that can run rodents through some of the tests they might experience in mazes — for example, they might receive an unpleasant puff of air in one place, but not others. Each corner can also be keyed to respond only to specific animals, so that different rodents undergo different tests.

At $60,000, the IntelliCage system holds 16 mice. The ability to keep multiple mice in one cage is a plus, notes behavioural neuroscientist David Wolfer of the University of Zurich in Switzerland, because they are social animals. "Housing them together helps lower stress, which is a source of variability in the data." That said, because it is based on RFID tags, IntelliCage recognizes fewer behaviours than video, Wolfer says. For instance, it cannot detect when an animal rears up on its hind legs. But Oettler counters that video analysis is more open to observer bias in terms of interpreting results.

WATCH WHAT YOU EAT

Behavioural scientists have also automated dietary monitoring. Kravitz, for instance, investigates obesity by tracking mouse food intake and activity levels. But because mice eat very little, even tiny mistakes in measurements can throw results off, he says. That's where automation comes into play.

Automated hardware from firms such as Research Diets in New Brunswick, New Jersey, and Sable Systems International in North Las Vegas, Nevada, uses miniature electronic scales to measure each animal's consumption. But it can have a high price-tag, making studies of many animals at once economically impractical. So Kravitz and his co-workers developed an open-source alternative: the Feeding Experimentation Device (FED).

Designed to fit in a standard cage, FED uses an animal's RFID tag to document its behaviour, logging every time a mouse takes a food pellet. Each device costs roughly $350 to build, less than one-tenth of the price of commercially available systems.

Instructions are available on OpenBehavior, a site co-founded by Kravitz that is dedicated to open-source behavioural-science projects. But, cautions Kravitz, do-it-yourselfers are usually on their own if the system has technical hiccups. "You build them yourself. They're cheap to build, but how cheap depends on how much your time is worth," he says.

RODENT IPADS

At Western University in London, Canada, cognitive neuroscientists Tim Bussey and Lisa Saksida have developed chambers containing touchscreens, which researchers can use to test rodents on 20 or so cognitive tasks, covering memory, learning, attention and even gambling.

"It's like having an iPad for a mouse or rat," Bussey says. "The main difference is that where a human would touch their finger to the screen, a mouse would bring their nose to their screen." Successful completion of a task causes a built-in food-well to dispense drops of strawberry milkshake.

The touchscreens come preprogrammed with tasks from Campden Instruments in Loughborough, UK, and Lafayette Instrument in Indiana. Alternatively, researchers can use software called the Animal Behavior Environment Test System to program their own tasks, says Bussey.

Because the tasks are standardized, data can be compared across labs, or even species, says Brandon, who uses the devices in his research. The aim is to place information from many labs in one database so that the community can tell what neurons are doing in structures across the brain during certain tasks. "The amount of data we can collect blows my mind."

And that volume of data is growing. Brandon is now coupling touchscreen chambers with open-source 'miniscopes' that use fluorescence imaging to record neural activity in freely moving mice for about $500 per microscope. The chambers can even be integrated with optogenetics, experiments that use light to manipulate neural activity, he says.

And some firms are pushing automation even further, with fully automated habitats that allow around-the-clock monitoring, for instance to expand knowledge of the effects of a drug. TSE's PhenoWorld system, for example, houses several RFID-tagged rats or mice in multiple arenas, mazes and floors for experiments. It simultaneously records metabolic and other traits of the animals; a system for a whole colony might cost $800,000, says Oettler.

Similarly, researchers at MazeEngineers are building the 'Labyrinth', a grid of up to 25 modules that can be configured into more than 20 automated mazes. Housing units for rodents could be attached to the Labyrinth's edges, and automatically let animals in and out. "My dream is that the Labyrinth can run by itself," says He.

If that becomes reality, mazes might go from being tools of science to acting like scientists themselves. ■

Charles Q. Choi *is a freelance science writer in New York City.*