

In all of the AbES iterations, Merabet says blind volunteers such as Buchanan are active consultants whose feedback is crucial. Recently, these volunteers began providing another type of feedback: images of their brain activity. For more than a decade, neuroscientists have studied the brains of sighted people as they've learned to navigate mazes or played video games inside MRI machines or PET scanners. Merabet is now studying whether the brain activity of blind people doing these puzzles differs.

As all of his subjects have been blind since birth, the visual cortex, which makes up 30% to 40% of the brain's cortical surface, has never received visual stimulation. In the past decade, however, researchers have found numerous ways that brains of the blind repurpose this "real estate:" the region is active when they read Braille, interpret language, and localize sounds, to name just a few.

The team has adapted AbES so that the subjects can play it inside an fMRI scanner. Given the previous data on brain-region repurposing, it wasn't a surprise to Merabet that the visual cortex of his blind subjects' brains was active during game playing. His team is now trying to dig up some more specifics. As a volunteer plays the game, the scanner records brain activity continuously. When the player encounters a monster or stops to figure out where he is in the maze, AbES time-stamps the event. This allows the researchers to determine exactly which parts of the brain are actively making navigation decisions at that point.

The researchers' early results suggest that at these junctures, sighted players generally use the memory center, the hippocampus, to remember where they are and decide what to do. But it is at these decision points that blind players' visual cortices activate most robustly. The researchers plan to test people who became blind late in life, to determine whether the adult brain's wiring is still malleable enough to use the visual cortex in this way.

The addictive nature of computer games has provided the researchers with willing test subjects. When he opens the fMRI scanner after a session, Merabet says he often finds the volunteers still playing AbES. "Just a few more minutes. I need to finish this level!" they plead, he says. The blind students at Carroll Center are even competing to see who can collect the most jewels, he has heard. "Blindness is so isolating," Buchanan explains. "Being able to play games, that's the best."

—SARA REARDON

## EPIDEMIOLOGY

# Outbreak Detectives Embrace The Genome Era

Doctors could soon be sequencing bacterial samples from virtually every patient. The avalanche of data will help fight disease outbreaks, scientists say

Ten years ago, the U.S. government embarked on an unprecedented effort in forensic science: sequencing an entire microbial genome. The push came just weeks after 9/11, when a series of anthrax-laced letters killed five people and spread terror on the East Coast. The FBI decided it was worth knowing the full-length sequence of the *Bacillus anthracis* strain used in the attacks—all of its 5.2 million base pairs.

At the time, the first anthrax genome project was under way; taking on another one was an extravaganza possible only because no expense was spared to solve the crime. "We literally had more money than God to throw at this problem," says microbial geneticist Paul Keim of Northern Arizona University in Flagstaff, enlisted as an expert by the FBI. The sequencing alone cost about half a million dollars, Keim says. (The effort led investigators to a flask at an Army lab that the FBI says was the most likely source of the strain.)



**DNA sleuths.** The sequencing of anthrax bacteria from the 2001 mail attacks was a first in forensic science

Since then, the cost of sequencing an anthrax genome has come down by three orders of magnitude, to under \$500. Sequencing machines are becoming ever faster, smaller, and cheaper—spreading beyond big centers into clinics and small labs. And now, Keim and other genomic epidemiologists say, it's time to use the technique to track microbial movements on a global scale.

By routinely sequencing bacterial samples—perhaps up to a billion a year—scientists could pinpoint the sources of new outbreaks faster, determine whether a bug is

resistant to antibiotics, and investigate how public policies or the use of certain drugs change the course of microbial evolution.

Four weeks ago, 25 scientists gathered in Brussels for 2 days to discuss how to mobilize such a massive effort and dream about the benefits it would offer. Participants concluded that the world needs a global system to share and mine genomic data for microorganisms. It could be operational in 5 to 10 years, they say—but there are some formidable obstacles.

### Really scary outbreak

Currently, many U.S. and European labs use pulsed-field gel electrophoresis to identify strains of bacteria. In that system, microbial genomes are cut up by various restriction enzymes and separated on a gel. Scientists then estimate the size of the fragments and use the pattern to fingerprint a particular strain. But technology has moved on: "Imagine what kind of phone or computer you were using 15 years ago, and that is where pulsed-field gel technology is," Keim says.

Whole-genome sequencing can give better, faster answers about organisms, says Jørgen Schlundt of the Center for Genomic Epidemiology (CGE) at the Danish Technical University in Copenhagen, who organized the meeting. In January 2010, for example, scientists at the Wellcome Trust Sanger Institute in Hinxton, U.K., showed that by sequencing and comparing genomes of methicillin-resistant *Staphylococcus aureus*, they could track the global spread of the dangerous pathogen, document its likely emergence in Europe in the 1960s, and follow its spread within one Thai hospital.

In some cases, the genome can already deliver information in real time, as a threat emerges. When a deadly outbreak of enterohemorrhagic *Escherichia coli* hit northern Germany earlier this year, a group led by Dag Harsmen at the Münster University Clinic in Germany and another team at the Beijing Genomics Institute in Shenzhen, China, sequenced the strain responsible within days. The data gave scientists insights into the natural history of the *E. coli* strain and partly explained its virulence, but doctors battling the epidemic weren't helped much.

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Whole-genome sequences were immediately helpful, however, during an outbreak of *Klebsiella pneumoniae* that emerged a few weeks later in a hospital in Rotterdam, the Netherlands. The *Klebsiella* Oxa48 strain was “really scary” because it was resistant to all antibiotics except colistin, an old drug rarely used today because it is highly toxic to the kidneys, says Hajo Grundmann, an epidemiologist at the Dutch National Institute for Public Health and the Environment in Bilthoven.

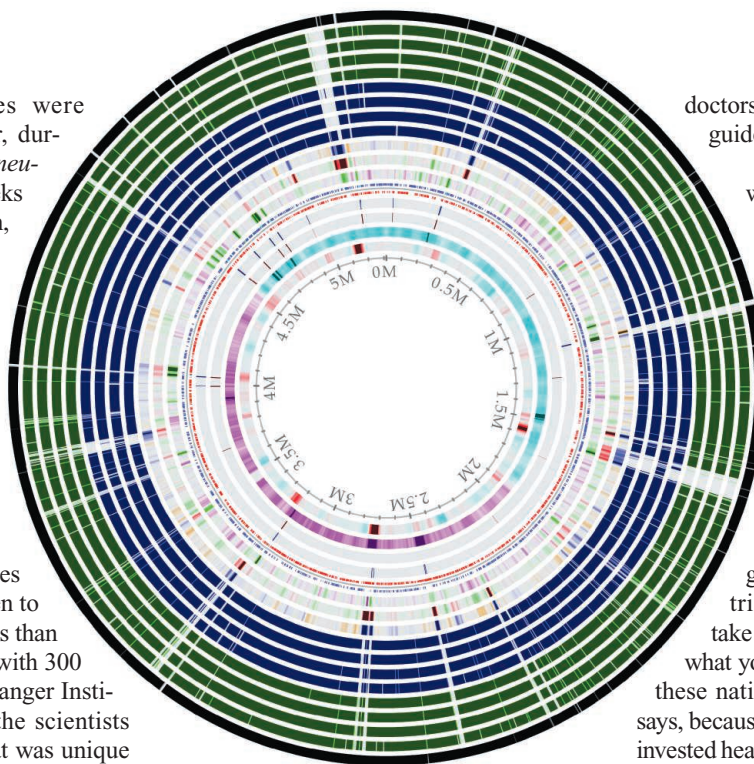
Grundmann chose two isolates and sent the samples to Harmsen to be sequenced; the work took less than 2 days. By comparing the data with 300 *Klebsiella* sequences that the Sanger Institute had recently completed, the scientists identified a stretch of DNA that was unique to the outbreak strain. They used it to develop a quick test that was then distributed to hospitals around the country, enabling doctors to screen incoming patients for the dangerous bug. “As far as I know, this was the first time that this technique was used almost in real time and had an immediate medical benefit,” says CGE head Frank Aarestrup.

But modern microbe hunters have bigger dreams. Rather than using genomics once an outbreak is under way, they would like to be able to detect an outbreak in advance. “You can literally think of this as a way of predicting global events in the sense of a weather forecast,” Grundmann says.

### Bioinformatics for dummies

To make all this possible, researchers need not just sequences of outbreak pathogens but data to compare them with. In the current cholera epidemic in Haiti, for instance, scientists quickly got their hands on *Vibrio cholerae* microbes from Haitian patients and sequenced them at several U.S. labs. They had some data pointing to U.N. peacekeepers from Nepal as the most likely source. But it took months to get recent samples from Nepal to provide DNA evidence of the link.

That’s why the Brussels meeting produced a road map, to be released soon, for the construction of massive worldwide genomic databases for many different diseases. Doctors who get patient samples sequenced in their labs would have them analyzed by a global or national server; at the same time, the sequence would be deposited in the database and be available for use in an emergency or for ongoing health research.



**Painting by genes.** This genome atlas compares the protein sequences of four *Klebsiella pneumoniae* genomes isolated from patients in a Danish hospital (green) and four older sequences (blue) with a reference genome (black). Deletions in the isolates are easily visible as gaps in the circles.

Another problem arose with Haiti’s data, says Keim, head of the pathogen-genomics division at TGen, a nonprofit research institute. In his lab in Arizona, he sequenced 24 Nepalese strains of *V. cholerae* but couldn’t compare them with a Haitian strain sequenced by a Harvard University group because they had used a different machine; the raw data weren’t compatible. That’s why harmonization was one of the big topics in Brussels. “You can almost think of this as the entertainment industry getting together to decide on Blu-ray as the standard for high-definition video,” Keim says.

Genomic epidemiologists agree that their field will blossom only if doctors get involved; without them, there will be no samples and no sequences. To give doctors incentive to upload sequence data, Aarestrup and others envision a system that will give back a plain-language report about the pathogen at hand. It could describe virulence factors, candidate antibiotics, and other isolates it resembles—“bioinformatics for dummies,” Harmsen says.

The Danish government recently awarded Aarestrup and others a €6 million grant to establish a proof of concept for the data-sharing scheme, which now provides information on the pathogen species and type. By November, Aarestrup also hopes to offer

doctors a resistance profile, which could guide the choice of antibiotics.

Doing this on a global scale will be a challenge. The system might have to absorb up to a billion genomes annually, or a billion gigabytes of data. CGE has a team working on this. For ideas, they are looking to gaming servers that routinely exchange huge amounts of data. The final host, they say, should be a neutral organization such as the World Health Organization.

Eventually, the system could greatly benefit developing countries, where infectious diseases take the biggest toll. And contrary to what you’d expect, it might be easier for these nations to transition to it, Schlundt says, because U.S. and European centers have invested heavily in databases using older technology. A global genomic database could also help break down barriers between biologists studying different groups of pathogens and between experts in veterinary medicine, food safety, and human health. “A bacterium is a bacterium whether you find it in foods, animals, or humans,” Aarestrup says.

To make the best use of a digital database, scientists will need more than just the genome sequence. The age, symptoms, travel history, and diet of a patient might be relevant as well. Handling these so-called metadata will bring a whole new set of problems, however. Keim suspects that Scandinavian countries, which routinely collect and store these types of data, might be among the early adopters. “I do not see the United States taking a lead on this,” he says. “We have excellent genomic technologies, but integrating it into the health care system will be a lot more difficult than in a country such as Denmark.”

Another major question is who will contribute data and how much. Countries don’t always share outbreak information—for instance, because they worry about hurting trade and tourism—and scientists sometimes hoard data until they have a paper in print. “This is a huge issue,” Schlundt concedes. “Everybody agrees that you should share strains and data, but it does not always work that way.” Funding agencies and scientific journals could play a big role in forcing scientists to share all data, he says—and they should. “Here we have this amazing technology that could really benefit global health. It is only for us to mess it up.”

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