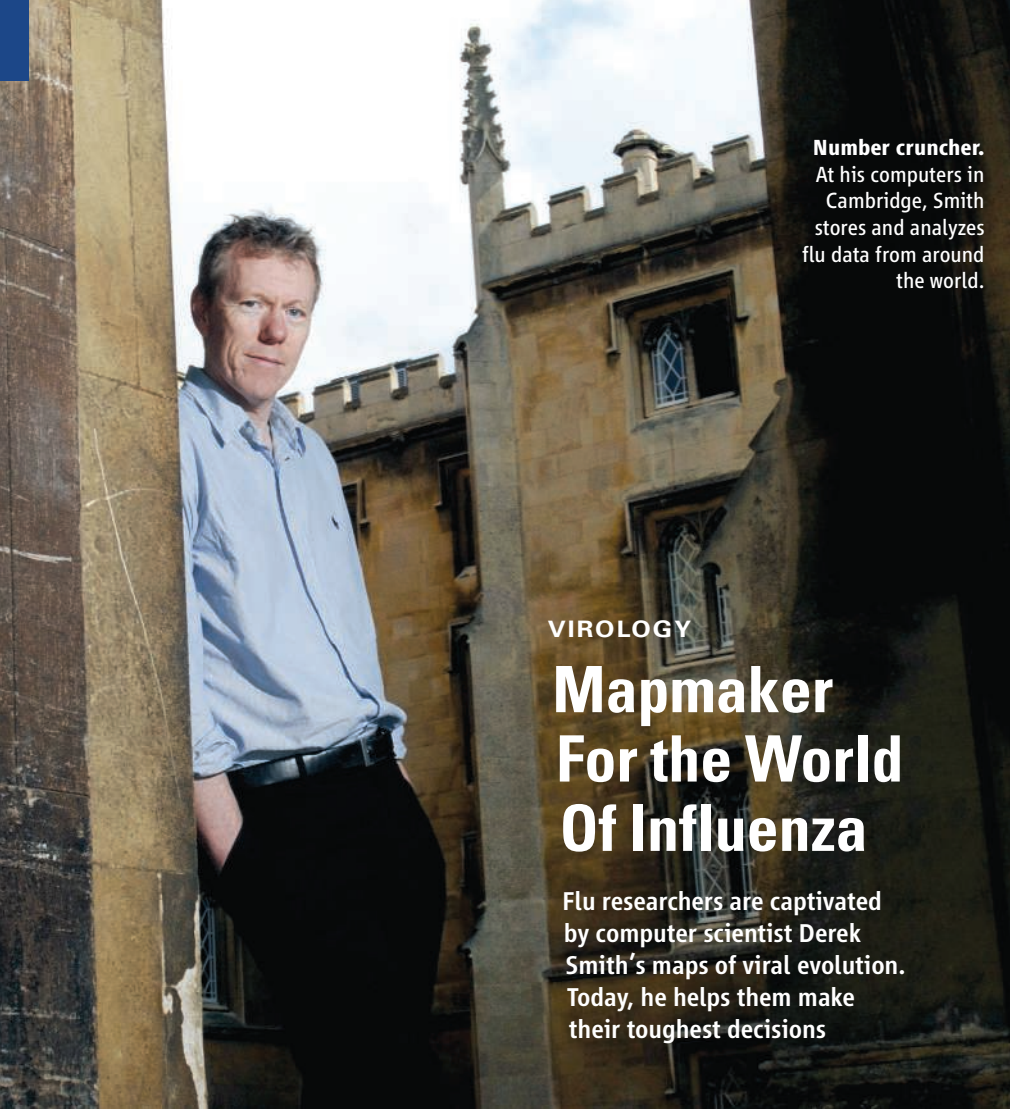

Number cruncher. At his computers in Cambridge, Smith stores and analyzes flu data from around the world.

VIROLOGY

Mapmaker For the World Of Influenza

Flu researchers are captivated by computer scientist Derek Smith's maps of viral evolution. Today, he helps them make their toughest decisions

DEREK SMITH DIDN'T WANT TO DO ROCKET science—literally. That's how he ended up becoming an internationally recognized expert in influenza virus evolution.

In 1992, at age 33, Smith was working at a research lab of Texas Instruments (TI) in Dallas, a company he had joined a decade earlier, fresh out of a British university. He specialized in the mathematics of speech recognition. One day, a colleague noted that the integrated circuits Smith was developing might play a key role in the control systems for an antiradar missile called HARM that TI was producing for the Pentagon. The missile needed to discern real radar stations from decoys, a problem not unlike detecting subtle differences in spoken words.

"I'm not a pacifist," Smith says, "but I didn't want anything to do with work directly related to the military." Instead, he started looking for a job in which his expertise might benefit public health. He found it in a Ph.D. project to model the immune system's recognition of influenza viruses at the Santa Fe Institute in New Mexico.

He never regretted the choice. Now at the University of Cambridge, U.K., Smith has become the unofficial cartographer of the influenza world. He has developed a technique to produce colorful maps visualizing the never-ending changes in the influenza virus, and over the past 4 years, his lab has become a global nerve center that analyzes influenza data from around the world. His work offers scientists a way to track the virus' evolution almost in real time, says Ian Barr of the World Health Organization's (WHO's) Collaborating Centre for Reference and Research on Influenza in Melbourne, Australia.

Indeed, influenza researchers find Smith's "antigenic cartography" so enlightening that, shortly after he and others published the first results in 2004, he was asked to join the select group that huddles at WHO's headquarters in Geneva, Switzerland, twice a year to decide which strains to put in the annual influenza vaccine that protects 300 million people. "It's a huge responsibility," he says.

From tables to maps

Influenza viruses elude the immune system by changing the shapes of the glycoproteins on their coat—in particular, hemagglutinin (HA), the one that latches onto human cells and to which our immune systems produce antibodies. That's why a flu shot or a natural infection one winter may not protect the year after.

To tell how much a new strain differs from previous ones, researchers test how well its HA is inhibited by antibodies to known strains harvested from infected ferrets. If the antibodies bind well, the new virus is "antigenically close" to those earlier ones; if they don't, the new strain is more distant. These results are used to create complex tables with thousands of numbers, each describing the outcome of one binding assay; they are impenetrable to all but the most experienced researchers.

Smith wanted to turn the tables into clear, accessible maps. Just as mathematicians can reconstruct a decent map of a country from the distance table in the back of a road atlas, it should be possible to map influenza strains based solely on each strain's antigenic distance from the others, he says. So in 1999, Smith teamed up with Alan Lapedes, a mathematician at Los Alamos National Laboratory in New Mexico, who, with Robert Farber, had laid part of the theoretical groundwork for such maps.

He also struck up a collaboration with Ron Fouchier, a virologist at the Erasmus Medical Center in Rotterdam, the Netherlands. When Fouchier switched from HIV research to influenza in 1998, he, too, had been struck by the opacity of the binding assay tables. "I thought there had to be a better way," says Fouchier. The Rotterdam lab also had 3 decades' worth of data and samples—precisely what was needed to produce a map. Of the three influenza types now circulating in humans, the trio picked H3N2, which changes the fastest and affects the most people.

The project was a gamble, says Smith; several groups tried before but failed to get the mathematics right. Even after they produced the first maps, the researchers spent several more years checking the results before publishing.

In the 16 July 2004 issue of *Science* (p. 371), they finally published a map of 273 virus strains that had been isolated since H3N2 emerged in 1968. The map is like that of an archipelago, and the strains come in clusters: Very often, the virus changes little from one year to the next, but occasionally, it makes a major antigenic jump, starting a new cluster, for which existing vaccines offer no protection. The jumps can't always be predicted from the viruses' genetic sequence, because a small change in the *HA* gene can sometimes cause a major shape change in the glycoprotein that makes antibodies lose their grip.

Smith had already presented his results to

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Coming Out of Asia—Year In, Year Out

Where does the flu virus hide when there's no flu? That question has puzzled epidemiologists for decades. Every place on Earth has an influenza season, usually the winter, when conditions are best for its spread. But what happens after that? Does the virus lurk in a few people until next year? Or does it disappear and come back, and if so, where from?

Using data about some 13,000 seasonal flu samples from around the world, Derek Smith of Cambridge University in the U.K. and colleagues provide an answer in this issue of *Science* (p. 340): A small number of countries in East and Southeast Asia "seed" the yearly epidemics washing over the planet. "It's really a fantastic paper," says Keiji Fukuda of the World Health Organization (WHO) in Geneva, Switzerland. It shows that strengthening surveillance in Asia is crucial, Fukuda says.

There were plenty of theories on what happens during influenza's absence. Some believed the virus remained in every country, hiding in infected but symptom-free people, or is passed on at rates too low to detect, only to roar back when winter comes around. Others believed it vanished, moving back between the northern and southern hemispheres, for instance, or receding temporarily into tropical Asia, Africa, and South America.

For the new study, Smith and his colleague Colin Russell first analyzed an antigenic map (see main text) of some 13,000 samples of H3N2, the most important flu type currently circulating. They discovered that changes in the virus always occur first in countries in East and Southeast Asia. That doesn't necessarily mean that the area acts as a source; the virus might also be evolving in parallel around the globe, with Asia being ahead of the curve by a couple of months.

But an analysis of the strains' hemagglutinin genes showed that flu epidemics in Europe, North America, and Australia are actually seeded by countries such as Japan, Thailand, South Korea, and Singapore. Europe and North America then act as conduits to South America, which has less direct contact with Asia.

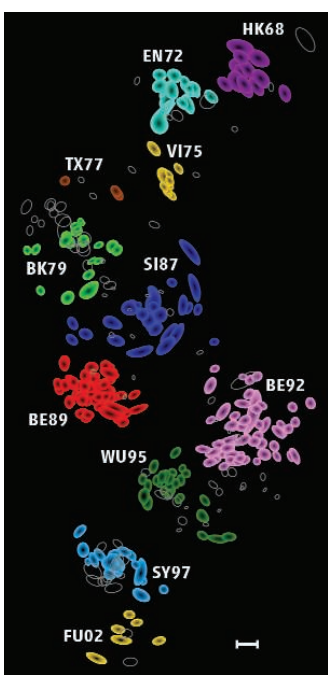
A study by Edward Holmes of Pennsylvania State University in State College and colleagues, published online by *Nature* this week, also shows that yearly waves in the temperate regions originate in the tropics. But that paper—based on a whole-genome analysis of 1302 strains from New York and New Zealand—does not pinpoint the source.

So what makes East and Southeast Asia special? A variety of climate zones in a small area creates a network of countries with overlapping flu seasons, Smith says. Frequent human travel gives the virus a chance to jump from one country to another. When winter arrives in Europe and the United States, strains from the Asian network spread to those continents aboard jumbo jets. But further, fine-grained studies will be needed to clarify exactly how the Asian network works and whether a similar network exists in India, as Smith and Russell hope to find out together with Indian scientists.

–M.E.

some members of the WHO panel; the invitation to join the group followed just 2 weeks after the *Science* paper was published. "All of us could see this was an emerging technology which had immediate application for the work we were doing," says Barr, a member of the group.

Smith's maps increase the group members' confidence that they're making the right choice, says WHO influenza expert Keiji Fukuda; they're also helpful for those less familiar with the tables, he says, such as vaccine producers, regulatory officials, and scientists who don't specialize in influenza. "They can look at these maps and go: 'Oh, now I understand it,'" Fukuda says. Barr concedes that the math and computer wizardry Smith uses to produce his colorful maps go over most influenza scientists' heads. "It will take a while before we throw away our tables," he says.



Influenza archipelago. On an antigenic map, each virus strain isolated between 1968 and 2003 appears as a small blob. They occur in clusters (each given a different color), starting with Hong Kong '68. The scale bar represents one antigenic unit, a measure of how similar strains are.

CREDIT: SMITH *ET AL.*, *SCIENCE* 305, 371 (2004)

Sister labs

Meanwhile, Smith's career has taken off. The University of Cambridge made him a research associate in 2003 and a full professor in 2007. In 2005, he landed a $2.5 million U.S. National Institutes of Health Director Pioneers Award that enabled him to expand his research group to 10 members. He still spends a day a week at Fouchier's lab in Rotterdam, which he says helps keep him grounded in real biology. Some of their best ideas bubble up while the two indulge their shared love of Tom Waits and good whiskey, says Fouchier. Grad students and postdocs, too, are encouraged to cross the North Sea frequently. "We're really like sister labs," Smith says.

"Derek has a wonderful personality for bringing together people and data," says Nancy Cox of the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, one of the four WHO Collaborating Centers. Smith's close association with the Collaborating Centers has given him access to an unparalleled wealth of antigenic and genetic data from around the world, which enables him to study questions on a global scale, as a paper in this week's issue of *Science* (see sidebar, above) illustrates.

Aware of his privileged position, Smith is careful not to hog the glory, stressing the collaborative nature of the process and crediting the people who provide the data. "As a theoretical biologist, you have to be aware of your place in the food chain," he says. "I don't even know how to do a binding assay."

Now that his lab has come into its own, Smith hopes to tackle new problems. He would like to predict farther in advance which strains will be dominant in a given year. Currently, vaccine producers have just 8 months between the panel's decision and the start of the vaccination season, which means a yearly scramble. At the same time, Fouchier and Smith are trying to predict a strain's antigenic profile directly from its gene sequence; that might eliminate the need for those pesky tables altogether.

Smith also wants to expand the scope of his cartography. Maps for H1N1—the other influenza A virus circulating among humans—and for influenza B are under way. He has also started collaborations to work on agents such as rabies, malaria, and dengue and has plans to branch out into HIV. "There's no reason you can't do the same thing with many other pathogens," he says. One thing seems sure: The mapmaker has put himself firmly on the map.

–MARTIN ENSERINK

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