# Breathing Lessons

## *Biology and math come together to teach a computer to breathe*

By MICHAEL STROH

About four years ago, mathematician Satish Anjilvel at Duke University in Durham, N.C., received a phone call from James D. Crapo, a pathologist at the university's medical center. Crapo was directing a team of biologists studying the effects of pollution on the human body and needed to learn where particles such as dust and asbestos went once they enter the lung.

The pathologist had a problem. Conducting asbestos experiments on people was, of course, out of the question. Animal studies, on the other hand, would be unreliable, since lung shape — which determines where an inhaled particle might wind up — varies from one species to the next.

The solution: Crapo hoped to obtain a computer model that could simulate airflow patterns within even the tiniest structures of the human lung. Knowing that this would require some "pretty hefty mathematics," he wondered if Anjilvel would be willing to leave his teaching position in the math department and join the medical center to help create the model.

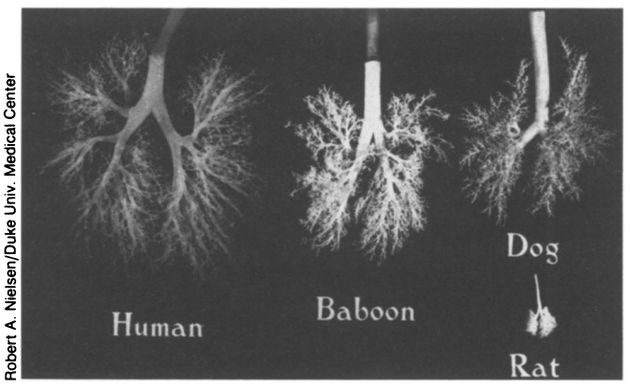
Anjilvel agreed. After all, the project sounded like a refreshing change from his normal academic diet of theoretical equations. "You could spend weeks trying to solve one and get nowhere," he says.

At the American Mathematical Society meeting last January in Baltimore, Anjilvel showed off the model that took four years to create: an animated, two-dimensional simulation of airflow patterns and pollutant dispersal inside the microscopic passages of the deep lung.

One difficulty in modeling the lung arises from its complex architecture. With all the blood vessels and tissue stripped away, the lung's airways resemble a leafless, upside-down tree. A short trunk (the trachea) diverges into two limbs (the bronchi). Shooting off from the bronchi are many crooked, tapering branches. Microscopic sacs called alveoli cluster like buds at the ends of each branch.

A pair of human lungs contains 300 million alveoli — a number greater than the population of the United States. If spread open, these sacs could cover the end zone of a football field. Alveolar walls are very thin and webbed with capillaries, allowing gases to pass back and forth between the lungs and the bloodstream.

Crapo wanted Anjilvel to focus his model on the alveoli and the tiny branches that feed them, because the pathologist's earlier research had suggested that contaminants strike the alveolar region especially hard. "The damage can be recorded long before any abnormality is noticed, long before you get emphysema or something like that, so it's important to understand why this part of the lung gets hit the worst," Anjilvel explains.



Robert A. Nielsen/Duke Univ. Medical Center

*The bud-like alveoli have been pruned off these lungs to show how airway geometry varies from species to species.*

Before he could start, Anjilvel needed a detailed blueprint of the deep lung, since its geometry would determine air patterns and thus a pollutant's trajectory. The alveoli and surrounding airways are notoriously difficult to measure with precision, but bioengineer Robert R. Mercer, another Crapo team member, had already developed a clever way to get these numbers.

Over the past 10 years, Mercer has studied lungs "from mouse to man." To measure the lung's microscopic structures, he uses a technique called serial section reconstruction. "We're probably the only lab to look into this technique as a quantitative tool," he says.

Mercer starts with a fresh, healthy lung specimen. Obtaining a fresh animal lung isn't a problem, but human specimens require more patience. "They're like hen's teeth," he says. "Someone who has a lung lobe that needs to be replaced and who wasn't a smoker is rare. We catch about one a year at this medical center."

Once Mercer has obtained a healthy sample, he embeds it in a material resembling Plexiglas and then cuts this "loaf" into 2,000 to 7,000 paper-thin slices.

Next, each slice gets photographed and digitized into a computer. Using these data, the computer can fit all the slices back together and display the lung in three dimensions. Now, says Mercer, "we can simulate taking a pair of calipers and making measurements from all sorts of directions."

Mercer has used serial section reconstruction to make the first precise measurements of some of the lung's tiniest structures, such as an acinus — a cluster of alveoli vented by a single airway. "You got a dime?" he asks. "If you look on the back of a dime you'll see this leaf cluster thing. That's almost exactly the size of an acinus in a rat. It's about five times larger in a human. Those numbers are my numbers. I've gotten them by doing the reconstructions."

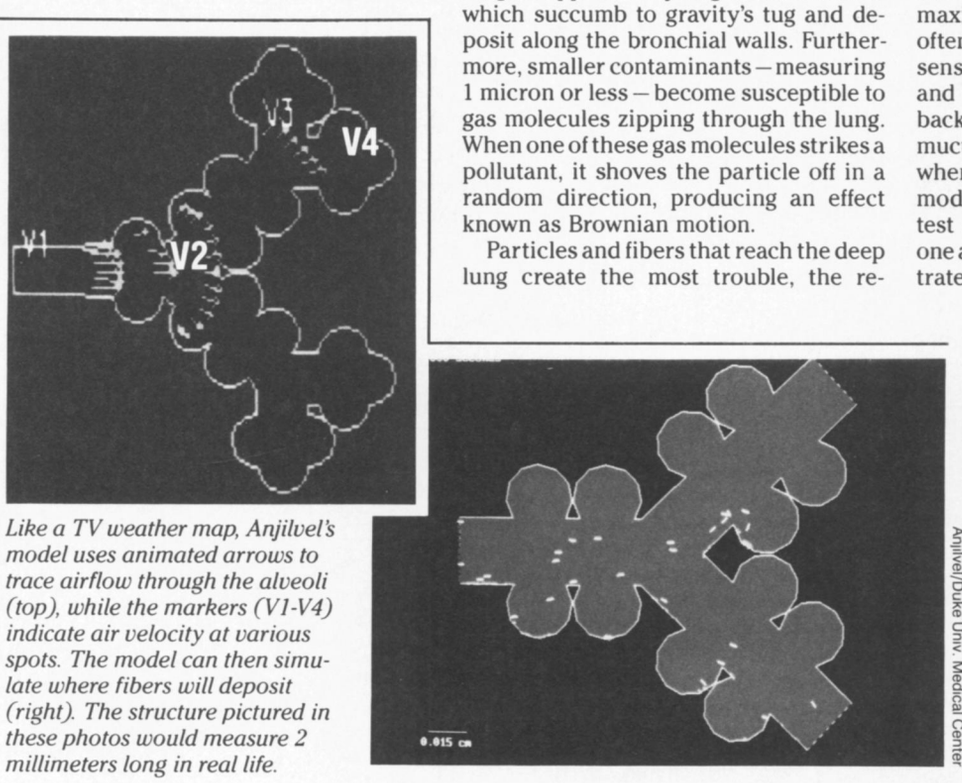
Because his reconstructions are so detailed and the lung so complex, Mercer hasn't measured the entire organ yet. But his data do include much of the deep lung, the area Anjilvel needs for his model.

Mathematical models that predict how many pollutant particles land in different parts of the lung aren't new, but earlier models provided only "mathematical

simplifications of the problem," says Anjilvel. "My model is aimed at predicting whether certain points of the deep lung are getting more dose than other points."

Accuracy means taking into account physiological features that earlier models ignored, such as the expansion and contraction of the airways or the opening and closing of the alveoli. "In the past, people would say, 'Yes, that's a phenomenon which has some effect,'" Anjilvel says, "But they couldn't say how much effect it had."

He calculates the forces inside the lung by using the Navier-Stokes equations, century-old formulas that describe fluid motion. "One advantage we have is that the actual calculation of deposition is entirely a physical process, not a chemical one," he says.




*Like a TV weather map, Anjilvel's model uses animated arrows to trace airflow through the alveoli (top), while the markers (V1-V4) indicate air velocity at various spots. The model can then simulate where fibers will deposit (right). The structure pictured in these photos would measure 2 millimeters long in real life.*

Anjilvel/Duke Univ. Medical Center

Even though Anjilvel and Mercer are still in the early stages of collecting information on deposition patterns, their simulation has already provided some interesting insights into what goes on as a contaminant makes its way through the lung.

Air moves briskly through the lung's upper passageways. Fibers and particles flow through the trachea at nearly 200 centimeters per second. At this speed, air boils with eddies, which jostle inhaled contaminants, sending many into the mucus lining the bronchial walls. This sticky substance traps the pollutants and prevents them from damaging the sensitive epithelial cells that grow underneath. Tiny, hair-like cilia that line the airways sweep contaminated mucus toward the mouth, where it's coughed out.

Anjilvel's model shows that contaminants often run into places where the airways branch. Like the guard rail that cleaves the off-ramp from an interstate, tissue sticks out at these junctions, making an easy target for contaminants. "Branches are a hot spot for particle deposition," says Anjilvel.

In the deep lung, the air begins to slow, moving less than 1 centimeter per second. At this velocity, air often can no longer support many large contaminants, which succumb to gravity's tug and deposit along the bronchial walls. Furthermore, smaller contaminants – measuring 1 micron or less – become susceptible to gas molecules zipping through the lung. When one of these gas molecules strikes a pollutant, it shoves the particle off in a random direction, producing an effect known as Brownian motion.

Particles and fibers that reach the deep lung create the most trouble, the researchers say, since only a very thin mucus layer covers the lower airways. In the alveolar region, the mucus vanishes altogether.

Anjilvel's model can pinpoint the exact spot where dust and asbestos attack the sensitive alveoli. "We're able to predict deposition on a microscopic scale, and that has not been done before," he says.

With more specific data about where contaminants hit the human lung, other members of Crapo's team can now use animal models to refine predictions about a contaminant's health effects. "If the rat gets 12 fibers and you observed a certain effect, then when the human gets 12 fibers [in the same place] you might expect to see the same effect," Anjilvel explains.

Understanding pollution's grip inside the lung has significant implications. Indeed, federal regulatory bodies like the Environmental Protection Agency have provided most of the funding for Crapo's research project. "Small changes in regulatory standards can cost millions or even billions of dollars to the economy as a whole," says Anjilvel. "But it works both ways. If your safety levels are too low, people are going to be hurt."

Moreover, he says, the new model could prove useful for applications other than pollution. In medicine, for example, many drugs used to treat lung diseases are administered with an inhaler, a device that contains a liquid medication suspended in an aerosol. Droplet size influences how well the drug negotiates the lung's airways.

"The question," says Anjilvel, "is what kind of aerosol droplet is ideal to get the maximum dose to the deep lung? Very often, drugs tend to get wasted in the sense that the patient breathes them in and then just winds up breathing them back out. Or they end up depositing in the mucus, instead of going to the deep lung where they're needed." Using a computer model like Anjilvel's, researchers could test different droplet sizes to see which one allowed the most medication to penetrate the lung.

In the future Anjilvel hopes to soup up his model on a supercomputer. The IBM workstation he's currently using takes hours to crunch through airflow and deposition computations.

"The simulations are kind of like movies," he says. "Using the calculated results, we can create images, store those images and play them back. Which means you can't change things on the fly. You can only show what you've already calculated."

He would also like to include the upper lung in the model. Already, another mathematician has signed on to attack the difficult calculations the group expects to encounter.

The Duke project exemplifies what many mathematicians consider an exciting new trend in their field: the application of mathematics to the life sciences. "The uses of mathematics in biology and medicine are just exploding," says Michael C. Reed, director of the Center for Mathematics and Computation in the Life Sciences and Medicine in Durham, N.C. "The Crapo group is one good example."

Anjilvel says he's enjoying life in the pathology division, although it required some adjustment at first. "I've been forced to explain fairly complex physical and mathematical ideas in ordinary English . . . without resorting to formulas, which is what mathematicians tend to do in moments of stress."

He believes the effort was worth it. "Biologists are getting to the point now where they need these sophisticated mathematical tools," he says, "and mathematicians are in the position to provide them." □