in monkey procurement seem like an old boys' network of people calling their friends," says New England's Johnson. "Two people may call up and get different information about availability."

In addition, one size definitely doesn't fit all researchers. Scientists have become increasingly selective as they develop more sophisticated research tools and reagents. But the cost of many of the animals produced through NCRR-funded breeding programs now far exceeds that budgeted in the average NIH-funded grant. Add in the rising demand from outside the AIDS field and the result, Robinson says, is that "lots of NIH grants depend on macaques, and [the researchers] can't get the monkeys they need."

Most in demand are monkeys that don't have chronic infections. In the early 1980s, coincident with the start of the AIDS epidemic, primate researchers discovered that many rhesus macaques had been infected with what is now known as simian retrovirus. Although the virus has no relationship to SIV or HIV, it can kill monkeys from an AIDS-like disease. Many animals also harbored an array of other viruses that could either harm the monkeys or their handlers, including STLV, herpes B, and foamy. So 12 years ago, NCRR decided to fund select primate centers and commercial outfits to breed "specific pathogen free" (SPF) animals.

Unfortunately, the SPF breeding program has done little to alleviate the crunch, and rising demand has driven up prices. Kay Izard, a zoologist who runs the SPF program at LABS of Virginia in Yemassee, South Carolina, says the top asking price for an SPF animal has risen from $2000 in 1987 to $5000 today. That's nearly double the per capita price budgeted by most NIH-funded researchers, some of whom buy as many as 100 rhesus macaques a year.

Three years ago, NCRR decided to phase out funding for the SPF breeding program. It was a tacit admission that the animals had become too expensive for academic researchers and that the program was instead subsidizing commercial users. "The long-range goal of NCRR was to set these colonies up and not to subsidize them forever," says Robinson. But Izard and others have questioned that decision. "It's too bad they didn't extend the funding for it, since there is a real problem," says Izard, noting that they have had to raise prices even higher since NCRR cut its support.

On top of the shortage of SPF animals, AIDS researchers are also hard pressed to find females of breeding age, as well as a specific genetic type used for immunologic studies that help explain why vaccines fail or succeed. Specifically, researchers have developed reagents that allow them to measure killer cells—a critical component of the immune system—only in animals that have a marker on their white blood cells known as Mamu-A*01. "The wait for Mamu-A*01 animals is not quantified in months but in years," says Johnson.

NCRR soon will solicit new proposals from monkey breeders, says Robinson, in hopes of boosting supply. But new housing for breeding colonies is also essential, says Ronald Desrosiers, who heads the New England center in Southborough, Massachusetts. "You can give me all the [breeding] money you want," he says, "but if I can't use it to build a building to put them in and the infrastructure to support it, it is impossible [to produce more animals]." Others suggest that centers in cold climates like New England should instead contract out the work to commercial firms in warmer climates, where animals can roam outside all year.

Some researchers see foreign stocks as a partial solution. Marta Marthas of the California Regional Primate Research Center in Davis says researchers should look more carefully at rhesus macaques still available from China. Although studies suggest that Chinese macaques naturally control SIV infection more effectively than do monkeys of Indian origin, Marthas says many questions remain about their differences. David Watkins of the University of Wisconsin, Madison, hopes to implant embryos from Indian Mamu-A*01 animals into Chinese rhesus mothers. "[In vitro fertilization] is the way to go," he says, although he adds that the technique is now inefficient.

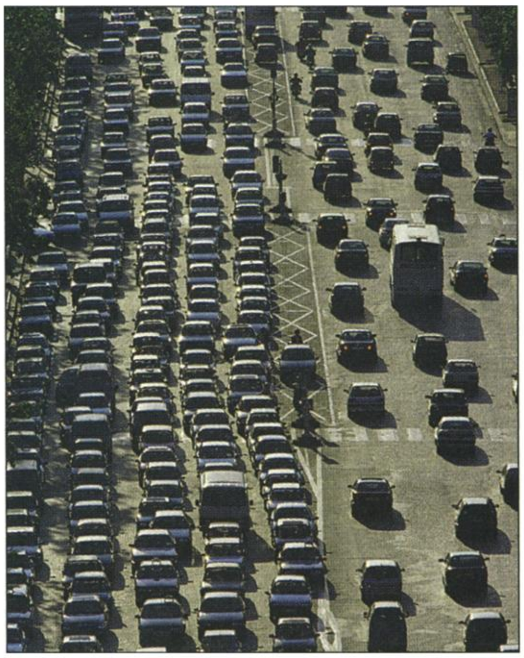
Whatever its cause, the shortage of rhesus macaques has highlighted the need for scientists to become more involved in breeding them. "What disturbs me the most is that this [issue] is looked at with great disdain by everyone," says Marthas. "We have to think ahead. If we don't, we'll jeopardize not only our own experiments but those of future scientists." —JON COHEN

STATISTICS

Revealing Uncertainties in Computer Models

Computer simulations give the impression of precision, but they are founded on a raft of assumptions. Making uncertainties evident is a tough challenge

As computers have become faster and smarter, scientists have used them to build models of complex phenomena—everything from wildfires on rugged terrain to traffic snarls on urban streets. These simulations can yield precise answers to problems a person with a pencil and paper would need millennia to solve. But just how reliable are these virtual solutions? Although the precise numbers and realistic pictures produced by computer simulations give an illusion of accuracy, a ravening swarm of assumptions, simplifications, and outright errors lurk beneath. New tools are needed, scientists say, to quantify the uncertainties inherent in calculations and to evaluate the validity of the models. But, as several recent uncertainty workshops* attest, the quest for such tools is itself an uncertain and challenging process.



A difficult road. To keep out of jams, modelers simulating complex systems such as traffic patterns must know the uncertainties involved.

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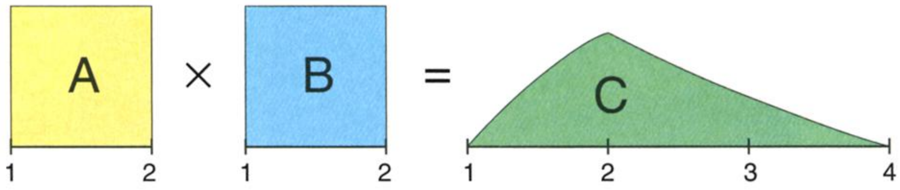
The worrisome scenario is not the old science fiction cliché of supersmart machines shucking the

* Two took place last December in Santa Fe and Los Alamos, New Mexico. A 2-day meeting on the "Evaluation of Complex Computer Models" (3 to 4 December) focused on how statisticians can address the problem, and a 3-day follow-up on "Predictability of Complex Phenomena" (6 to 8 December) looked at efforts currently under way.

shackles of humanity, but rather semi-stupid programs placed in positions of responsibility—a kind of digital Peter Principle, in which computers rise to their level of incompetence. As long as human experts act as a buffer between the program and the real world, interpreting the results and gauging their reliability, computer models can get by without built-in error estimates. But when the models are turned over to nonexperts, or when the programs themselves are authorized to make decisions—an automated inventory control system, for example, that decides when to restock items—quantifying their uncertainty becomes urgent. Much of the global warming debate, for example, is fueled by the radically different numbers that different models produce. As the explosive growth of computer power allows researchers to tackle ever-bigger problems with ever-more-complex models, even the experts have a hard time sorting the scientific wheat from the numerical chaff.



Keeping track. Even simple algebra gets tricky when the variables are probability distribution functions (pdf's). Here the product of two pdf's, each uniform on the interval from 1 to 2, is a combination of two logarithmic curves.

"We've been lucky in the past, because we've picked problems where the sources of uncertainty are negligible," says mathematician Mac Hyman of Los Alamos National Laboratory (LANL) in New Mexico. Regulating the flow of oil through the maze of pipes and pumps of a refinery, for example, is a straightforward exercise, as is designing a bridge. But problems like anticipating the impact of global warming up the ante on uncertainty. The number of variables is hugely greater, and the scale of the problems makes even state-of-the-art computers creak under the computational load. Moreover, notes Hyman, in a few decades, most complex computer simulations will predict not physical systems, which tend to obey well-known mathematical laws, but social behavior, which doesn't.

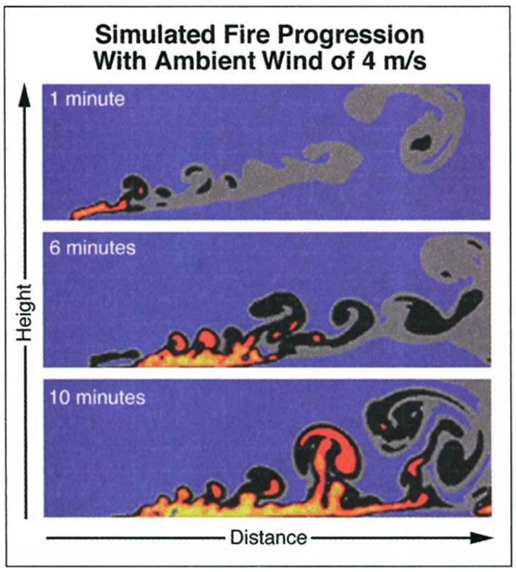
One mushrooming area of application is the Defense Department's "stockpile stewardship" program, which aims to maintain the reliability of U.S. nuclear weapons in part through computer simulations and virtual testing. "The consequence of making a mistake could be very, very high," says LANL physicist David Sharp—imagine detonators that don't comply with simulations after they've sat around for 50 years. And the need for quantifying uncertainty, Sharp emphasizes, goes beyond weapons, "pervading absolutely everything."

At the very least, modelers need to start putting error bars on their output, says Hyman, which is no easy task. Commonplace in reports of experiments, error bars show a range of values that is likely (or guaranteed) to include the "true" value. To calculate them, researchers must figure out the uncertainties in each step of the model and see how those uncertainties build on each other. Ultimately, however, the uncertainty enthusiasts would like to have a new variable type to work with when they write computer programs: probability distribution functions, or pdf's. The most famous and ubiquitous pdf is the bell-shaped Gaussian, or "normal," distribution, but there are many others. Unlike error bars, which merely give a range in which the solution should fall, pdf's attach a likelihood to each possible value. Current computer languages, which are based on algebra rather than statistics, make calculating with pdf's an awkward, ad hoc affair. That's one reason modelers stick to exact numbers even when they're only estimates, Hyman points out. Extending languages to handle pdf's more easily should help.

Error bars and pdf's won't just make results easier to interpret, notes Gregory McRae, a chemical engineer at the Massachusetts Institute of Technology. By pinpointing areas that need attention, they can also help researchers design experiments. For example, imagine a simple, two-step chemical reaction, A → B → C, with uncertain rates of reaction. A mathematical model that keeps track of uncertainties as it computes the three time-varying concentrations can indicate which experiments will be most informative. A big error bar in the model's output partway through the reaction tells the laboratory scientist to measure the three concentrations at the corresponding time.

But what's easy for a two-step process is well-nigh impossible for the highly complex systems that dominate modern modeling. "As we put more of our understanding into these models, it's getting harder to probe their uncertainties," McRae says. The trouble is, error estimates, when done at all, tend to be added as an afterthought, which makes them less accurate. "Since uncertainty is important, why not put it in at the beginning?" McRae asks.

That's where statisticians come in. "We need to be playing a bigger, more important role in working with the modelers," says Sallie Keller-McNulty of LANL. Statisticians, whose forte is variability, could help modelers come to grips with the noise of real-world data. In weather models, for example, there is a tremendous correlation between precipitation patterns in different locations, but it's easy to overlook without a statistical analysis. Statisticians could also help develop mathematical equations that describe inherently probabilistic features of physical systems, such as the distribution of grass, pine needles, and other fuel in a wildfire, or the way drivers behave in a traffic simulation.



Burning questions. With a broad range of variables—from weather to fuel chemistry—wildfire simulations blaze with uncertainties.

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Despite formidable hurdles ahead, the uncertainty crowd thinks modelers will eventually embrace error bars, pdf's, and other techniques of uncertainty analysis with much the same fervor carmakers now show in advertising safety features on cars. Scott Weidman, director of the Board on Mathematical Sciences at the National Research Council, sees a "very healthy sign" in the number of workshops devoted to uncertainty. "It's a sign of a maturing field that people can step back from individual problems and ask if there's a general methodology," he says. "People are starting to think of a metaproblem: how to build a better science of computer science."

–BARRY CIPRA