Abstractions

SENIOR AUTHOR
The ways in which proteins and RNAs fold and unfold, and the shapes they form, fascinate molecular biologists. Imaging techniques such as X-ray crystallography have provided snapshots of the molecules in their stable forms. And optical tweezers allow researchers to stretch out the folded molecules and watch them refold. But measuring the free-energy differences between folded and unfolded states using optical tweezers has proved problematic, as much of the energy measured dissipates as heat rather than as work done by the refolding molecule. Theoretical physicists have derived general fluctuation theorems that can be used to obtain the free-energy values for refolding. On page 231, Carlos Bustamante and his team provide an experimental verification for these predictions, and then use them to obtain RNA folding free energies. *Nature* caught up with Bustamante, the senior author on the paper, to find out more.

Why is it so hard to get at these molecules' folding free energy?
The molecules are very complex, and there is a catch 22. If you try to measure the energies accurately, it would take far too long. Alternatively, you can pull the molecules quickly, but then you lose the information about refolding energies.

How did you overcome this obstacle?
We tested the Crooks fluctuation theorem and then used it to extract the folding free energy of a molecule that dissipated a lot of energy as it refolded. The theorem passed the test with flying colours and we got the molecule's folding energy.

How many stretches did you have to do?
A few hundred pulls sufficed.

How broadly applicable is your technique?
It should be valid for most biological molecules.

What are the other authors up to now?
The first author, Delphine Collins, is at Merck, where she is working on nanobiotechnology projects. The work she did here at Berkeley was very interdisciplinary, so it served her well. The second author, Felix Ritort, is a professor at the University of Barcelona. I feel both happy and guilty that I converted a theoretician into an experimentalist. And Ignacio Tinoco, my colleague in the chemistry department, and I continue to work on the thermodynamics of small systems and single molecules.

You did 35 drafts before submitting this paper. Why so many?
I'm a little bit of an obsessive when it comes to wording. This is an abstract, somewhat difficult, subject and the challenge is to write something clear for the reader. ■

MAKING THE PAPER

Neil Ferguson

What would happen if a flu pandemic arose in Asia?

For his latest research, Neil Ferguson had to face an event that could spell disaster for the world. The epidemiologist at Imperial College London wanted to know what would happen if the avian influenza virus H5N1 mutated so that it could pass readily from human to human. How fast would the flu spread? What, if anything, could be done to stop a pandemic?

To find out, Ferguson, with fellow epidemiologist Don Burke at Johns Hopkins Bloomberg School of Public Health, and their colleagues, built the largest computer simulation of infectious-disease epidemics yet published.

The model simulated an outbreak starting in Thailand, so the first thing the team needed was detailed data on that country's population. "The sizes and locations of households, workplaces and schools, and how far people travel between each are key," Ferguson explains. Collecting these data and turning them into model parameters, such as how many people one person might contact in a certain time period, was harder than writing the program's code, Ferguson says.

The process was further complicated by a lack of background information. "We had to make some assumptions about how a new influenza virus would behave," says Ferguson. "These had to be based on what was seen in past influenza epidemics and pandemics." But that sort of information proved hard to come by. "Less detailed statistical work had been done on past pandemics than we hoped," Ferguson says. Making up for this shortfall was an important part of the team's research.

Once they had the data and the computer model, Ferguson and his team set out to make sure they covered all possibilities. They used 'sensitivity analysis', which involves running the model over and over again using different assumptions about unknown parameters, such as incubation times, and looking at how the outcome changes.

This meant running the model hundreds of thousands of times. To do these runs quickly, the model needed to be coded efficiently, and required computers with huge amounts of memory — 20 times that found on a typical PC. In fact, the team hooked up ten high-powered computers in parallel, but even then the final runs took more than a month of computer time.

The outcome (see page 209) was worth the wait. The team found that on average one person infected with a new pandemic virus might infect 1.8 other people, that people are likely to be highly infectious for only 1 or 2 days after they develop symptoms and, most importantly, that we have a chance of preventing a pandemic if we can detect the first few cases and act fast enough.

Ferguson says that the results argue for improving disease monitoring, creating international stockpiles of antiviral drugs and vaccines, and planning detailed strategies for a rapid response to suspicious clusters of human cases. The advanced online publication of the paper has already helped prompt Roche to stockpile drugs to enable the World Health Organization to tackle flu outbreaks using similar methods to those modelled by Ferguson's group.

Meanwhile, Ferguson and his team are working on a model of what would happen if containment failed and a pandemic spread from Asia to Europe and the United States. ■

QUANTIFIED **DAVID EISENBERG'S LAB**

A numerical perspective on *Nature* authors.
Communication is at the heart of David Eisenberg's lab at the University of California, Los Angeles. Through meetings, seminars and an active journal club, his team members swap ideas both among themselves and with other groups at the university.

Interactions, this time involving proteins, also form the core of the lab's scientific work. The team's latest findings show how proteins can string themselves together into huge fibres (see page 266). Eisenberg stresses the importance of self-motivation in working at his lab. He seeks co-workers who want to "press out the frontiers of knowledge", he says, and who are inherently curious about the fundamentals of protein interactions and their contributions to metabolism, as well as their failure in various diseases.

3 Number of papers from Eisenberg's lab published in *Nature* since 2000.

36 Number of years Eisenberg has led the lab.

1971 Year Eisenberg published his first paper from the lab (E. G. Heidner *et al. Science* **171**, 677–679; 1971).

18 Number of graduate students and postdocs working full-time in Eisenberg's lab. The lab shares another seven staff, who look after equipment, with other structural-biology groups.