NEWS

The code within the code

Computational biologists grapple with RNA's complexity.

One of the most beautiful aspects of the genetic code is its simplicity: three letters of DNA combine in 64 different ways, easily spelled out in a handy table, to encode the 20 standard amino acids that combine to form a protein.

But between DNA and proteins comes RNA, and an expanding realm of complexity. RNA is a shape-shifter, sometimes carrying genetic messages and sometimes regulating them, adopting a multitude of structures that can affect its function. In a paper published in this issue (see page 53), a team of researchers led by Benjamin Blencowe and Brendan Frey of the University of Toronto in Ontario, Canada, reports the first attempt to define a second genetic code: one that predicts how segments of messenger RNA transcribed from a given gene can be mixed and matched to yield multiple products in different tissues, a process called alternative splicing. This time there is no simple table — in its place are algorithms that combine more than 200 different features of DNA with predictions of RNA structure.

The work highlights the rapid progress that computational methods have made in modelling the RNA landscape. In addition to understanding alternative splicing, informatics is helping researchers to predict RNA structures, and to identify the targets of small regulatory snippets of RNA that do not encode protein. "It's an exciting time," says Christopher Burge, a computational biologist at the Massachusetts Institute of Technology in Cambridge. "There's going to be a lot of progress in the next few years."

"The splicing code is a problem that we've been bashing our heads against for years."

The floodgates were opened by high-throughput technologies that allow researchers to compile comprehensive catalogues of RNA molecules found in various tissues and under different environmental conditions. Such techniques revealed that 95% of the human genome is alternatively spliced, and that changes in this process accompany many diseases. But no one knew how to predict which form of a particular gene would be expressed in a given tissue. "The splicing code is a problem that we've been bashing our heads against for years," says Burge. "Now we finally have the technologies we need."

Blencowe and Frey's team used the masses of data generated by these technologies to train a computer algorithm to predict the outcome of alternative splicing in mice. Given the DNA sequence of a particular gene, the algorithm predicts which segments of that DNA sequence will be included in a final messenger RNA molecule in one of four tissue types: the central nervous system, muscle, the digestive system and embryos. The model works well, says Burge, and is an important technological advance. But he hopes that it will be refined to mimic more closely the mechanism that the cellular splicing machinery uses to make its choices.

Wiggle and jiggle

The sequence of letters in an RNA molecule is not the only determinant of how the molecule will function. Its three-dimensional structure can also affect how it interacts with other molecules, including drugs that are designed to target it. "RNA forms highly flexible structures that wiggle and jiggle just due to thermal motion," says Hashim Al-Hashimi, a biophysicist at the University of Michigan in Ann Arbor. "It is very difficult to define them as a static structure." Structures of the same molecule determined using various techniques sometimes look wildly different,

Nurse wants elite UK science focus

Less than 24 hours after being nominated as the new president of the Royal Society — Britain's national academy of science — Paul Nurse had already kicked off a controversy. In an interview published on 27 April in the British newspaper *The Times*, he argued for a more elitist approach to the funding of science. "You need a combination of special systems that attract and support those who are excellent," he said, "and rigorous reviews so that when they cease to be excellent, as many often are, they don't just hang on to those resources."

The interview (conducted before his nomination) riled many scientists in Britain, who are suspicious of concentrating limited resources on a few leading lights at the expense of the many. Nurse now says that his comments were not meant as an attack on the system as a whole. "The words didn't come out quite right," he says, before adding: "I do think there's a need to think about how one supports the very best science, which might need to be dealt with a little bit differently from the rest."

Speaking frankly is nothing new for the 61-year-old Nobel prizewinner. "Paul's quite opinionated," says Antony Carr, a biochemist at the University of Sussex, in Brighton, UK, who was a graduate student with Nurse in the mid-1980s. "Our lab meetings were fun but also a bit daunting at times," Carr recalls. "You were just waiting for him to tell you how it really was."

"He can be kind of intense sometimes," adds Emily Nurse, one of his two daughters and a high-energy physicist at University College London. In earlier years, she says, she and her sister received many lectures on topics ranging from science to history. "I've never known anyone to be so interested in things," she says.

Born into a working-class family, Nurse's straight talking and sharp scientific skills eventually won him the chair at the University of Oxford's department of microbiology in 1988. He took charge of the Imperial Cancer Research Fund in London in 1996, steering the fund through its 2002 merger with another charity,

J. HILL/*THE TIMES*/N.I. SYNDICATION

Paul Nurse has been nominated to be the next president of Britain's Royal Society.

the Cancer Research Campaign, into Cancer Research UK. Nurse was convinced that the charities would work better together than as competitors, and persuaded nervous scientists in both that the merger would be a success. In 2001, he shared the Nobel Prize for Physiology or Medicine for his

K. SWITAK/NHPA

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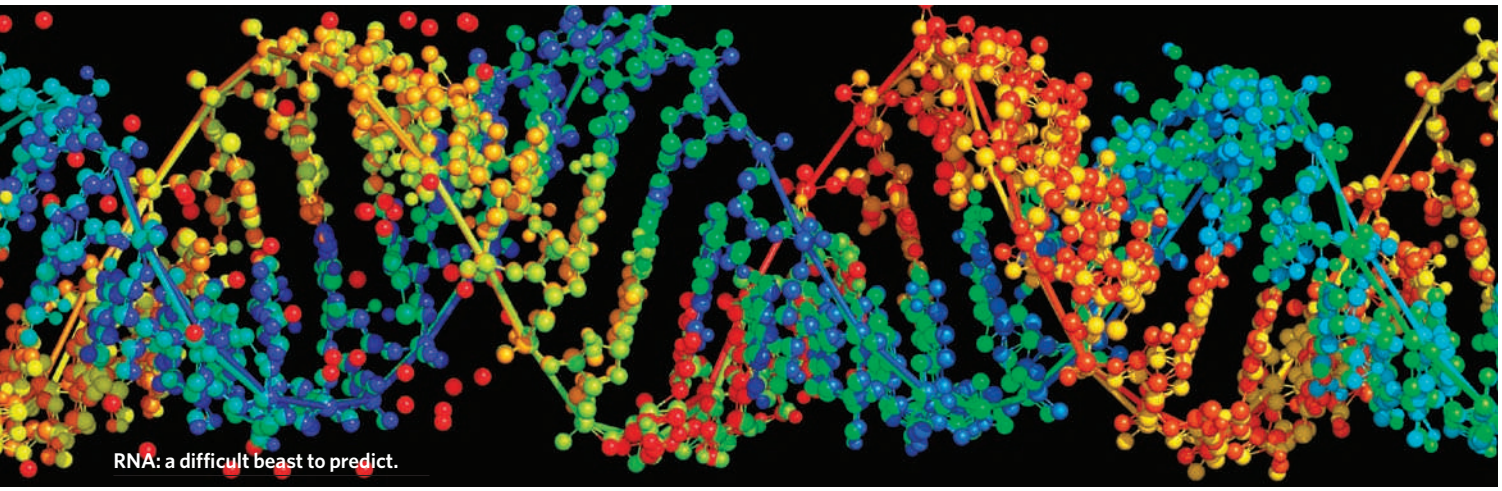

LAGUNA DESIGN/SPL

RNA: a difficult beast to predict.

Al-Hashimi adds, because RNA is sensitive to even small variations in its environment.

As a result, researchers including Al-Hashimi are eager to develop methods that will predict the three-dimensional structure of RNA on the basis of its sequence. At present, experimental techniques that reveal how an RNA molecule folds back on itself — its secondary structure — are fairly advanced. For example, in 2009, Kevin Weeks, a chemist at the University of North Carolina at Chapel Hill and his colleagues reported the full secondary structure of the HIV-1 genome — a strand of RNA about 9,000 letters long (J. M. Watts *et al. Nature* **460,** 711–716; 2009). Al-Hashimi has developed a method that combines such two-dimensional structures with knowledge of the constraints on RNA flexibility to predict aspects of the three-dimensional structure (M. H. Bailor *et al. Science* **327,** 202–206; 2010).

But automated programs for predicting three-dimensional structures are still quite limited in scope and need refining, says Tamar Schlick, a computational chemist at New York University.

Much of the enthusiasm for understanding RNA is motivated by the discovery of small RNAs that do not code for protein, yet can regulate gene expression. The hunt is on to catalogue these RNAs and their targets — a quest aided by advances in algorithm design and the accumulation of genome sequences. This allows researchers to search the vast stretches of non-coding DNA between genes: the conservation of sections in many species could suggest that they have important functions.

But enthusiasm for finding functional non-coding RNAs may be getting out of hand, cautions Sean Eddy, a computational biologist at the Howard Hughes Medical Institute's Janelia Farm research campus in Ashburn, Virginia. Teams have reported thousands of such RNAs, but few researchers have followed up to confirm exactly what these RNAs do, or whether the molecules are simply aborted mistakes made by the machinery that converts DNA to RNA.

For now, Burge says he is enjoying the ongoing renaissance in RNA informatics. "These new technologies have given me hope." ■

Heidi Ledford

See News and Views, page 45.

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work on the genetics of cell division in yeast and humans. Two years later he was made president of the Rockefeller University in New York.

While at Rockefeller, Nurse kept a toe on the other side of the pond. He heads the scientific advisory panel for the UK Centre for Medical Research and Innovation, a £520 million (US$780 million) biomedical research centre planned for the heart of London. Many of his peers say that a move to the top job at the Royal Society is a natural step.

"He was, I think it's fair to say, the obvious choice," says Robert May, a zoologist at the University of Oxford, UK, and a former president of the society. Nurse has the perfect blend of academic credentials and political clout for the job, May says. "He just ticks all the boxes."

Nurse's appointment will have to be confirmed by the fellows of the Royal Society on 8 July and he would not assume the post until 30 November. He says he is not yet ready to discuss his plans as president, but campaigning for greater support for the very best scientists in Britain is squarely on his agenda. The idea comes from his experience as a trustee of the Howard Hughes Medical Institute in Chevy Chase, Maryland, which gives top scientists long-term support to set up labs in their most productive years, rather than doling out money for specific research projects.

"The very best science might need to be dealt with a little bit differently from the rest."

In November 2009, the Wellcome Trust, Britain's largest non-governmental funder of biomedical research, unveiled a similar plan (see *Nature* 462, 145; 2009). Nurse says he would like to see something like this applied to government funding. He suggests that 100–150 leading researchers across all disciplines would receive enough money to fully fund their research, allowing them to hire staff and buy equipment. Their grants would be regularly reviewed to ensure that they were still producing work worthy of the support. Such a programme would cost only around £100 million to £200 million per year, he says, amounting to a few per cent of the UK government's science budget.

Despite the disquiet over Nurse's interview in *The Times*, Carr says that most researchers will be willing to at least hear Nurse out on this and other ideas. "People are a little nervous," says Carr, "but if you didn't have someone with opinions, then things wouldn't get done."

Nurse will certainly have plenty to do as president of the Royal Society, which the government consults on policy and funding issues. Cash will be a key issue following a general election on 6 May, when the incoming government looks set to cut public spending, including science funding. In April, Nurse signed a letter attacking the opposition Conservative Party's science policy and supporting the incumbent Labour government. But he insists that "there will be no problem with me working with whoever ends up in power. I would argue for science." ■

Geoff Brumfiel