them to measure kinetics is like using a slow shutter speed to photograph a galloping horse – everything blurs together in the image. This realization led the authors to use a pulsed femtosecond UV laser, which crosslinks proteins to RNA fast enough to capture kinetic parameters. They call their method KIN-CLIP (for kinetic CLIP).

To test the method, the authors applied it to an RBP called Dazl, which is required for the production of reproductive cells, and regulates gene expression[9]. Dazl binds to hundreds of target mRNAs, increasing their stability and the number of proteins produced[10]. However, despite its biological importance, much about the binding and function of Dazl is unknown, making it an ideal candidate for KIN-CLIP experiments.

Sharma and co-workers first verified that KIN-CLIP identifies RNA targets found in previously published data sets produced from 'snapshot' CLIP. They then calculated kinetic parameters, known as rate constants, for the association and dissociation of Dazl with each of its thousands of binding sites in RNA. These results revealed that Dazl binding is highly dynamic: its binding time is short; the RBP resides at individual sites for only a few seconds. Dazl also binds rarely, and so the binding sites are free of the protein for most of the time.

The authors also found that multiple Dazl molecules tend to bind at sites that are close together. The kinetic analysis suggests that this might be due to cooperative binding – a phenomenon in which the binding of one protein to one site increases the likelihood that other proteins will bind to nearby sites. Finally, the authors incorporated the newly determined kinetic parameters of Dazl into a predictive model of its impact on gene expression, thus providing a biochemical basis for its function and setting the stage for future research.

One of the most exciting aspects of this study is the potential of KIN-CLIP for studying other RBPs, but the method does have some limitations. For instance, as with all CLIP-based techniques, the ability to crosslink the protein of interest to bound RNAs is a requirement; this can prove challenging, because some proteins do not have the necessary side chains properly oriented for crosslinking. The biggest hurdle, though, for potential KIN-CLIP converts is that specialized equipment is needed for the crosslinking: pulsed femtosecond lasers might not be easily accessible for many biologists. Furthermore, the experimental procedures and associated analysis of KIN-CLIP libraries are more complicated than are those of standard CLIP experiments, and might prove to be another barrier to adoption.

Nonetheless, this study has brought the tools of biochemistry into living cells, and, in doing so, might provide an inflection point in the study of RNA–protein interactions. The next step is to apply KIN-CLIP to other RBPs, but the prospect of bringing it to bear on other types of interacting biomolecule also glitters on the horizon. Indeed, the authors intriguingly note that pulsed femtosecond lasers can crosslink proteins to DNA – perhaps a 'DNA KIN-CLIP' is within reach. Sharma and colleagues have not just set a new standard in RNA biology, they might have also unleashed the power of biochemistry on molecular biology more generally.

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Quantum information

A step closer to optical quantum computers

Ulrik L. Andersen

A programmable photonic circuit has been developed that can execute various quantum algorithms and is potentially highly scalable. This device could pave the way for large-scale quantum computers based on photonic hardware. **See p.54**

Quantum computers promise to deliver enormous computational power and solve problems that cannot be tackled by ordinary (classical) machines. There are many hardware platforms on which quantum computing can be developed, and it is not yet clear which technology, or combination of technologies, will prove most successful. Today, the leading schemes are based on superconducting electrical circuits or trapped-ion technologies. Another approach, based on photonics, has often been considered impractical because of difficulties in generating the required quantum states, or transformations of such states, on demand. However, this method could turn out to be the dark horse of quantum computing. On page 54, Arrazola *et al.*[1] report the development of a programmable and scalable photonic circuit, and demonstrate three types of quantum algorithm on this platform.

According to quantum theory, there is an inevitable uncertainty associated with the amplitude and phase of any state of light (the phase specifies in which stage of an oscillation cycle the light wave is). If this quantum uncertainty is unequally distributed between the amplitude and phase, the state is said to be squeezed; and the more the state is squeezed, the more photons it contains. Multi-photon squeezed light is found in many quantum-optics experiments, and quantum-computing models based on these states have existed for more than two decades[2,3]. However, whether computers based on such models would be practical has been justifiably questioned, because of the quantum uncertainty.

This scepticism has disappeared in the past few years. It became clear that a relatively simple optical circuit, based solely on squeezed light, beam splitters (devices that split beams of light in two) and photon counters, could carry out a sampling algorithm (a procedure that takes a random sample of data) at a speed beyond the reach of classical computers[4]. It was also discovered that such an algorithm has many practical applications[5]. For example, it is useful in simulating transitions between states of molecules[6] and finding matching configurations of two molecules – a process known as molecular docking[7].

In the computing architecture used to implement this quantum sampling algorithm, squeezed states of light are generated and launched into an optical network consisting of several optical paths and beam splitters (Fig. 1). The squeezed states mix together when they meet in beam splitters because of a quantum effect called interference. As a result, all the states come out completely scrambled, in a way that depends on the relative lengths of the optical paths, known as their relative phases. Reprogramming these phases alters

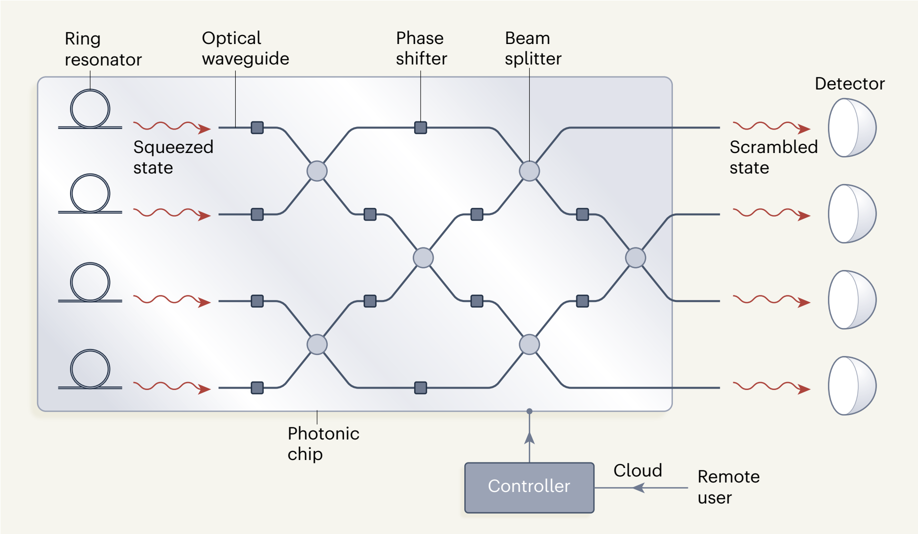

Figure 1 | Quantum algorithms implemented on a photonic chip. Arrazola *et al.*[1] carried out an experiment using a photonic chip, a highly simplified illustration of which is shown here. On the chip, devices called ring resonators produced quantum states of light known as squeezed states. These states were launched into an optical network consisting of optical waveguides (structures that direct light) and beam splitters (devices that split beams of light). The squeezed states became mixed together when they met in the beam splitters, and all the states were completely scrambled when they left the network. Finally, highly sensitive detectors counted the number of photons in each scrambled state. The authors used their chip to execute quantum algorithms in which the input squeezed states represented input variables and the number of photons in each scrambled state represented the output achieved when the algorithm processed those variables. The chip could be reprogrammed to run different algorithms by using a controller to adjust the beam splitters and to manipulate devices called phase shifters. The controller could be accessed by a remote user through the cloud.

the type of scrambling. After scrambling, the number of photons in each output of this quantum circuit is counted using highly sensitive detectors.

The measurement outcome provides a specific sample of data from the quantum experiment. For a classical computer, the time needed to take such samples scales exponentially with the number of input squeezed states (amounting to billions of years when this number is high). By contrast, the quantum circuit can produce a sample in fraction of a second, demonstrating what is called a quantum advantage.

Arrazola *et al.* implemented their photonic circuit on a silicon nitride chip that is compatible with the fabrication processes used by the semiconductor industry. The authors produced a squeezed state in each of four micrometre-sized devices known as optical ring resonators on the chip using an effect called four-wave mixing. They achieved light propagation and interference by carefully etching tiny structures known as optical waveguides on the chip. The network of beam splitters was fully controllable and was made fully reprogrammable for a remote user through the cloud. The output of the network was then directed to four photon-counting detectors, and these detectors generated the samples that were sent to the remote user.

The authors executed different types of measurement to characterize the quality of the squeezed-light sources and the overall performance of the chip. First, they measured the uncertainty suppression of the squeezed states relative to ordinary states to be about 84%. Second, they measured the temporal purity of the states (a property that is crucial for successful interference in the network) to be 85%. Third, they carefully tested the quality of the interference. And finally, they verified that the samples generated had a genuinely quantum nature by testing them against a criterion for non-classicality – a necessary condition if the device, when scaled up, is to produce samples that are impossible to simulate using a classical computer.

In addition to the sampling algorithm used to demonstrate a quantum advantage, Arrazola and colleagues implemented two algorithms of greater practical relevance: one that determines energy spectra for transitions between molecular states, and another that finds the similarity between mathematical graphs that represent different molecules. The authors achieved this feat by encoding the specific problem into the squeezed states and beam-splitter network, and then using the samples generated to estimate the molecular spectra or classify the graphs.

Quantum sampling based on squeezed states has been demonstrated by other research groups[8–10]. In particular, one group last year ran the sampling algorithm on 50 squeezed states in 100 optical paths, and reported a quantum advantage[10]. The researchers estimated that it would take 600 million years to simulate such an experiment on a supercomputer. However, these demonstrations were not scalable because of the bulkiness of the set-up[8,10] or owing to photon losses[9]. Moreover, the circuitry of these previous experiments was not reconfigurable, and therefore only a single, random algorithm could be executed. By stark contrast, Arrazola and colleagues' circuitry is programmable and potentially highly scalable.

Nevertheless, there are still some hurdles to overcome before the quantum-sampling algorithm can reach its full potential and become useful for real-world applications. For instance, the quality of the squeezed states must be markedly improved, and for some applications, the degree of squeezing and the amount of optical power in each squeezed state must be individually controlled. Moreover, to scale up the system, photon losses need to be decreased; otherwise, the photons will not survive their journey through the circuitry.

Without doubt, the authors' demonstration of quantum sampling on a programmable photonic chip using highly squeezed states is remarkable and represents a milestone in this field. However, the number of commercial applications that can be implemented using the current architecture is limited. Completely different platforms are required to run heftier algorithms, such as Shor's algorithm for factoring large numbers into prime numbers[11], in an error-free manner. Fortunately, such platforms (also based on squeezed states) have been proposed[12,13], and their implementation constitutes the next step towards constructing a full-blown optical quantum computer.

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