genes associated with cell-cycle progression and a higher expression of the proliferation marker protein Ki67, compared with CTCs that were not associated with neutrophils. This cell-cycle-progression profile might indicate that neutrophil-associated CTCs are already primed to proliferate when they reach a secondary site.

The authors also identified pairs of inflammatory cytokine molecules and their corresponding receptors that defined CTC–neutrophil clusters. For example, CTC-associated neutrophils expressed the cytokines IL-1β and IL-6, and neutrophil-associated CTCs expressed the corresponding receptors for these cytokines. The authors found that *in vitro* exposure of mouse breast cancer cells to IL-1β and IL-6 increased their capacity to form lung metastases in mice. And when gene-editing was used to prevent the expression of the receptors for these cytokines in mouse cancer cells, expression of Ki67 was reduced in the neutrophil-associated CTCs. These findings suggest that communication between CTCs and neutrophils promotes the metastatic potential of the cancer cells.

A theme that has emerged in studies of the interactions between immune cells and cancer cells is the idea that the mutational profile of tumours can shape their crosstalk with immune cells[9]. Szczerba *et al*. indeed observed that patients with neutrophil-associated CTCs have a different spectrum of mutations in their cancer cells from that found in the cancer cells of patients without neutrophil-associated CTCs. One of the frequently observed mutations in tumour cells of people with breast cancer who had CTC–neutrophil clusters was in the *TLE1* gene, and the presence of this mutation in mouse cancer cells was shown to enhance cluster formation between CTCs and neutrophils. How mutations in *TLE1* affect clustering is unknown. The authors also discovered that the cell-adhesion protein VCAM1 is essential for clustering between CTCs and neutrophils in mice.

Several mechanisms have been reported[5,7,10] by which neutrophils can promote metastasis, including by protecting cancer cells against attack by immune cells, or supporting cancer cells in their invasion of another tissue. Szczerba and colleagues add a new mechanism to the list: the possibility that neutrophils support cancer cells in their journey through the bloodstream to secondary sites.

The authors' results suggest that interrupting the formation of CTC–neutrophil clusters might offer a strategy for preventing metastasis, and that the mutational profile of the primary tumour, such as the presence of *TLE1* mutations, could indicate which patients are likely to develop CTC–neutrophil clusters and thus might benefit from cluster-disrupting therapeutic interventions.

Looking ahead, several key issues should be addressed before attempts are made to target CTC–neutrophil clustering in the clinic. Most crucially, it remains to be determined whether neutrophils cause the increased metastatic potential of CTCs, or instead tend to cluster with CTCs that have a high metastatic potential. Although neutrophil depletion inhibited the formation of lung metastases in Szczerba and colleagues' study, this approach not only blocks CTC–neutrophil clustering, but also prevents other pro-metastatic functions of neutrophils. One way of specifically investigating the connection between neutrophil–CTC clustering and metastasis could be to trace the fate of CTCs that have been genetically engineered to lack VCAM1, thus interfering with their ability to associate with neutrophils. Would such CTCs be able to make it from their primary site to a secondary site, and, if they could, would they be unable to proliferate or be eliminated by immune cells?

Another central issue is to define the window of therapeutic opportunity for interventions that target CTC clustering with neutrophils. It is not known whether neutrophils and cancer cells cluster in the primary tumour and then enter the bloodstream together. Also unknown is whether detection of CTC–neutrophil clusters in the blood signifies that other neutrophil-associated CTCs have already established metastases. A suitable system in which to address these matters would be genetically engineered mouse models of cancer that recapitulate the stepwise progression of cancer in tandem with coevolving immune-cell responses. Such animals would provide a more faithful model of the course of progression of human cancer than the mouse models used by Szczerba and colleagues, which were mainly immunodeficient.

Szczerba *et al*. have provided important insights that are relevant to the growing body of work indicating how neutrophils promote metastasis and how CTCs interact with other types of blood cell. As we learn more about the cellular interactions that affect metastasis, we could be moving closer to generating much-needed treatments to stop cancer in its tracks. ■

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QUANTUM PHYSICS

New ways to encode and use quantum bits

Quantum computers require controlled encoding to protect computations from environmental noise. Two experiments have achieved such encoding using what are known as infinite-dimensional quantum systems. SEE LETTERS P.509 & P.513

ALESSANDRO FERRARO

Transmitting or manipulating information in a noisy environment typically requires some form of encoding and error correction. If these precautions are necessary when information is carried by classical physical systems, they are even more so when the carriers are fragile quantum systems. However, quantum encoding is notoriously difficult, because the laws of quantum mechanics impose severe constraints — for example, a single quantum object cannot be copied, which hinders simple encoding schemes. Consequently, the manipulation of encoded quantum systems, which is necessary for error correction, can be extremely involved. On pages 513 and 509, Flühmann *et al.*[1] and Gao *et al.*[2] report promising methods for encoding and manipulating quantum information using, respectively, the state of motion of a trapped ion and the state of multiple photons in superconducting cavities.

Quantum systems can be classified into two categories, depending on the dimensionality of the parameter space that is needed to describe their features accurately. On the one hand, there are quantum features that require a finite dimension. An example is the magnetic moment of an electron, which has only two distinguishable states and is therefore represented in a 2D space. Such features

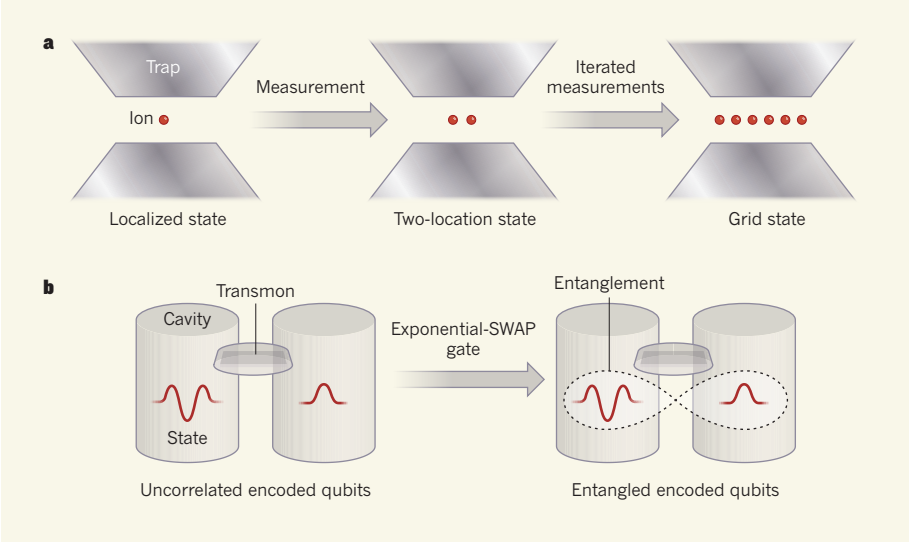

Figure 1 | Encoding and manipulating quantum bits (qubits). **a**, Flühmann *et al.*[1] report an experiment in which a single ion is prepared in a localized quantum state in an electromagnetic trap. A measurement of the system causes the ion to become delocalized in two distinct locations. Iterating these measurements leads to the ion being delocalized in a grid. The authors show that these grid states are a good approximation of a long-sought type of encoded qubit called a GKP-encoded qubit[5]. **b**, Gao *et al.*[2] present an experiment in which two superconducting cavities are coupled by a superconducting electrical component known as a transmon. A qubit is encoded in the state of the microwave field contained in each of the cavities. The authors demonstrate an operation called an exponential-SWAP gate[8] that causes these two states to become entangled (correlated in a non-classical way). Crucially, this operation works regardless of the way in which the qubits are encoded.

are called discrete variables, and they are intrinsically digital[3]. On the other hand, there are quantum features that have infinitely many distinguishable states, such as the position of a quantum harmonic oscillator — the quantum-mechanical version of a mass suspended on a spring. These features are known as continuous variables and are intrinsically analog[4].

From the transmission of data over the Internet to data analysis, classical information is typically encoded in digital form because of the existence of robust digital error-correction schemes. Therefore, when it comes to quantum information, it is natural to consider discrete-variable systems, such as two-state systems called quantum bits (qubits). This approach has been well explored in the past few decades. However, error correction remains challenging, and it ultimately requires a single logical qubit (a qubit that can be used for programming) to be suitably encoded into many physical qubits (actual implementations of qubits). In other words, it is necessary to enlarge the dimension of the space, and the choice of discrete-variable systems then turns out to be not so obvious.

Consequently, various methods have been proposed for encoding a logical qubit into the infinite-dimensional space offered by a single continuous-variable system, rather than by many discrete-variable ones. A celebrated continuous-variable encoding is the Gottesman–Kitaev–Preskill (GKP) scheme[5], which was proposed in 2001. A crucial feature of this scheme is that most encoded operations (manipulations of logical qubits) belong to a set of operations that, in general, can be easily implemented[6]. However, a method for generating GKP-encoded qubits has been elusive. Flühmann and colleagues have succeeded in this endeavour by preparing a quantum harmonic oscillator in a state that resembles a GKP-encoded qubit. They used an architecture consisting of an oscillator in the form of an atomic ion that is free to oscillate along one axis of an electromagnetic trap.

The authors' technique involves two steps (Fig. 1a). First, the ion is confined in a state of motion that has a well-defined position in the trap, using a technique that exploits energy loss to reduce the uncertainty in the ion's motion[7]. Second, a sequence of measurements is taken using laser pulses, after which the ion is delocalized in specific regions of the trap, akin to a grid. Flühmann *et al.* managed to prove that these grid states are a good approximation of a GKP-encoded qubit. Importantly, they found that such encoded states could be manipulated at will, achieving fidelities (a measure of the similarity of quantum states) of 87–97%.

As mentioned, GKP encoding is not the only option, and other schemes exist that can be more convenient, depending on the system at hand. It is therefore desirable to be able to manipulate logical qubits using operations that are independent of the encoding. An example of such an operation is the exponential-SWAP gate[8] (the exponential function of the operation that swaps two logical qubits), which was proposed in 2016. A crucial feature of the exponential-SWAP gate is that any algorithm can be run

50 Years Ago

Apollo 9, which was launched on February 28, will go through the motions of a landing on the Moon but in the comparative safety of an Earth orbit. The enterprise involves the first testing in space of the lunar module which is to ferry men from the command module to the lunar surface and back again. The trials include a manned flight of the lunar module on a trajectory of the kind planned for the Moon landing. The pilot of the lunar module will go outside for two hours, and during their 150 orbits of the Earth the three-man crew will have ample practice at shuttling between the two spacecraft. Most of the activity which makes Apollo 9 NASA's busiest manned mission yet is crammed in the first five days of the ten-day flight. This is to ensure that as many as possible of the more important tests are carried out if the flight has to be cut short. The remainder of the mission is as much as anything an endurance test to verify that the spacecraft systems — and the men within them — can last the duration of a trip to the Moon and back.

From *Nature* 1 March 1969

100 Years Ago

Mr. T. A. Joyce describes in the January issue of *Man* a remarkable wooden stool recently acquired by the British Museum from the island of Eleuthera, Bahamas. Objects of wood from the West Indies are by no means common, and specimens from the Bahamas are exceedingly rare. From one of the shorter sides of the seat of this chair projects a knob, which has been carved to represent a grotesque human head, of which the eyes and mouth have evidently at some time been emphasised by inlay, probably of shell. These State chairs were used for a honorific purpose, for chiefs and other distinguished persons.

From *Nature* 27 February 1919

by repeated use of the operation, interspaced with other operations that act on single logical qubits only. Gao and colleagues realized the exponential-SWAP gate in an architecture composed of superconducting cavities that contain microwave fields and that are coupled and measured using superconducting electrical components called transmons.

In the authors' experiment, logical qubits are encoded in the states of multiple photons in two cavities — another infinite-dimensional system (Fig. 1b). Gao *et al.* realized two different encodings: Fock encoding, which is based on the number of photons; and coherent-state encoding, which uses the superposition (summation) of particular quantum states called coherent states. Notably, the latter encoding was previously shown to extend the lifetime of a logical qubit beyond what is achievable using any of its physical constituents alone[9]. On the basis of the experimental techniques that were developed to extend the lifetime, Gao and colleagues demonstrated the exponential-SWAP gate by implementing a controlled exchange of photons between the two cavities. Crucially, this operation is deterministic, and works with both Fock encoding and coherent-state encoding, reaching fidelities of 85% and 60%, respectively.

These two experiments demonstrate two cornerstones of quantum computation using continuous variables: GKP-encoded qubits and the exponential-SWAP gate. Even if the current set-ups do not yet reach the quality required for a fully fledged error-correction scheme, they represent a major step towards this objective. In particular, improvements are required to increase the lifetime of the encoded qubits and to allow the possibility of concatenating many levels of error correction. A common trait of the experiments is that they use ancillary discrete-variable systems to manipulate the continuous variables. Hybrid continuous and discrete schemes can therefore, in principle, be devised to improve the performance of both experiments[10].

Besides full error correction and large-scale computation, which are probably still some distance away, the techniques developed in these studies could have other applications. For example, GKP-encoded qubits can be used for high-resolution displacement sensing[11], whereas exponential-SWAP gates integrated in a circuit might enable the demonstration of specific instances in which quantum computation outperforms its classical counterpart[12]. More generally, the exquisite level of control attained in these two very different architectures shows that infinite-dimensional systems, despite their analog character, are a cutting-edge contender in the race for advanced quantum information processing. Scientists now have a remarkable source of inspiration to see what could be achieved using other emerging continuous-variable architectures, such as optomechanical and electromechanical systems and integrated optics. ■

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CARDIOVASCULAR BIOLOGY

Fresh twist in a biochemical whodunnit

Nine years ago, the compound kynurenine was reported to be responsible for the dilation of blood vessels during a potentially fatal inflammatory condition. New evidence has now identified the true culprit. SEE LETTER P.548

DAVID A. KASS

In the life-threatening condition known as sepsis, the body responds to infection by inducing widespread biochemical changes that make the situation worse, some of which can lead to a severe decline in blood pressure. Several molecular factors that alter the constriction of blood vessels are involved in this decline, including nitric oxide, prostaglandins and oxidants such as hydrogen peroxide. In 2010, kynurenine — a metabolic product of the amino acid tryptophan — was identified[1] as another factor that causes blood vessels to widen during sepsis. Stanley *et al.*[2] (who work in the same laboratory as the researchers who identified kynurenine) now say on page 548 that they got the wrong culprit.

Stanley and colleagues' work begins as a classic whodunnit. The authors found that carefully purified kynurenine often did not cause blood-vessel widening (vasodilation) of isolated blood vessels in the context of inflammation, despite the previous report[1]. However, they consistently observed vasodilation using a mixture of tryptophan and either the enzyme indoleamine 2,3-dioxygenase 1 (IDO1) or singlet oxygen, a reactive oxygen species that is generated by IDO1. The expression of IDO1 is normally low in cell types other than immune cells, but can be upregulated by inflammatory proteins known as cytokines and by redox stress[3,4] — which means that IDO1 is often expressed in the presence of oxidants.

Both IDO1 and singlet oxygen are involved in the production of kynurenine from tryptophan (Fig. 1a), but also in the making of other metabolites. The authors' findings therefore suggested that another vasodilator was being formed. They hunted it down, and found it to be a compound that they call *cis*-WOOH (Fig. 1b), which is formed by IDO1 in a reaction involving tryptophan and singlet oxygen in the presence of hydrogen peroxide.

IDO1 activity is conventionally thought to be stimulated by chemical reducing agents and inhibited by hydrogen peroxide[5]. By contrast, Stanley *et al.* found that reducing agents did not generate *cis*-WOOH in their system, whereas exposure to hydrogen peroxide did. In a series of clever chemistry experiments, the authors showed that: in the presence of hydrogen peroxide, IDO1 generates singlet oxygen, followed by *cis*-WOOH; the oxygen atoms that are added to tryptophan to form *cis*-WOOH are derived from singlet oxygen rather than hydrogen peroxide; and both IDO1 activity and singlet oxygen are required for tryptophan to elicit vasodilation.

In the previous work from the same group[1], kynurenine was reported to dilate blood vessels by causing the signalling molecule cyclic guanosine monophosphate (cGMP) to activate an enzyme called protein kinase G1α (PKG1α, which has a dimeric structure assembled from two identical protein monomers). Stanley and co-workers observed that vasodilation mediated by *cis*-WOOH needs much less cGMP than does blood-vessel relaxation mediated by kynurenine, but still requires activation of PKG1α.

The authors determined that *cis*-WOOH activates PKG1α by oxidizing a specific cysteine amino-acid residue (Cys 42) in the enzyme. This causes a disulfide bond to form[6] between the Cys42 residues in the monomers of PKG1α. This oxidation has also been reported to stimulate the enzyme's activity in a