stereotyped behavioural sequences that involve multiple body parts, such as bringing the hand to the mouth in a gesture that resembles eating a piece of food[9].

Gordon and colleagues re-examined motor-cortex organization in humans using a brain-imaging technique, called functional magnetic resonance imaging (fMRI), that indirectly measures neural activity through regional changes in blood flow. The authors imaged spontaneous activity in the brains of people lying motionless at rest. They also analysed subjects performing motor tasks (bending limbs in particular ways, for instance, or making certain noises in response to a cue), carefully mapping the topography of body movements to activity on the cortical surface. Their findings reconcile and build on previous observations.

Their main discovery is that, in contrast to the conventional depiction of the homunculus, the motor cortex is divided into alternating subregions that serve different functions (Fig. 1b). Most recognizable are the three 'effector' motor regions representing the foot, hand and mouth. Gordon *et al.* provide some evidence that — as in monkeys — these regions have a concentric arrangement. Lying in between them are three 'inter-effector' regions, which are very different from the effector regions.

The authors showed that, unlike effector regions, inter-effector regions are functionally interconnected, seemingly operating as a unit. Their activity is coupled with a set of brain regions called the cingulo-opercular network that is involved in goal-oriented cognitive control. During subject-initiated actions, inter-effector regions responded to the movement of various body parts — particularly during movements linked to visceral functions, such as swallowing, and to postural changes, such as shoulder movements. These regions even responded to the planning of movements that were never executed. The researchers observed none of these features in the effector regions.

On the basis of these findings, Gordon and colleagues hypothesize that inter-effector regions contribute to the preparation and implementation of actions, and effector regions to performing those actions. They dub the inter-effector regions collectively the somato-cognitive action network (SCAN).

This hypothesis will raise eyebrows and could spur a broad reconsideration of the homunculus model. Some researchers might question whether results based on fMRI — a blood-based imaging signal for which the precise neural basis is never clear — should override a model of the motor cortex based on direct cortical stimulation. This is a legitimate concern. However, Gordon *et al.* address this criticism by drawing together diverse lines of support.

For example, the authors reanalysed data from the 2020 electrostimulation study[4], and discovered that a sizeable region of the motor cortex from which no body movements could be elicited matched one of their inter-effector subregions. They replicated their main findings in large, publicly available fMRI data sets. They also found evidence for the inter-effector regions in infants, indicating an early developmental origin, and to some degree in macaques, indicating evolutionary conservation in primates. Finally, it is worth noting that a human electrophysiological study published on the preprint server bioRxiv[10] has described an area embedded in the motor cortex where neural responses to body movements resemble those seen in the inter-effector regions reported by Gordon and colleagues.

The work also has implications beyond the need to revise the functional layout of the motor cortex. Unlike in laboratory experiments, where studies of motor actions often involve simply flexing individual joints, real-world behaviours involve highly orchestrated movements that take into account gravity, energetics, social context and more. It is interesting to speculate that the connections that expand primates' control over their motor system[5,11] are matched by a parallel expansion of projections from inter-effector regions that control postural and visceral functions during the execution of behaviours.

There is perhaps some irony in deriving principles of natural movement control from the brains of subjects lying supine and motionless. But Gordon and colleagues have done just that. Their identification of the SCAN and its selective communication with the cingulo-opercular network opens the door to new ways of thinking about how the brain's motor circuits keep our entire body in mind as we carry out our daily activities.

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Quantum information

Superconducting qubits cover new distances

Marissa Giustina

Superconducting quantum bits, a promising platform for future quantum computers, have been entangled over a separation of 30 metres, with a performance that enabled the demonstration of a milestone in quantum physics. **See p.265**

Of the many physical platforms being explored for quantum computing, superconducting quantum bit (qubit) processors have stood out over the past decade for increases in their qubit number and system performance. For example, researchers have built superconducting quantum computers with up to a few hundred qubits, and have used superconducting qubits to run a number of quantum algorithms, including modelling physical systems and correcting quantum errors to pave the way for useful quantum computing. However, these qubits encode quantum information in tiny amounts of energy stored in circuit elements that must be cooled to millikelvin temperatures, and transferring quantum information between processors is challenging.

On page 265, Storz *et al.*[1] report a superconducting qubit set-up that operated over a 30-metre distance with high fidelity. Their approach involves a quantum property known as entanglement, which is a key ingredient in a possible strategy for transferring quantum information. The authors also show fast readout of the qubits' states, enabling them to demonstrate an experimental feat known as a 'loophole-free' Bell experiment, in the first successful attempt using superconducting qubits.

Quantum theory was conceived to reconcile observations that were at odds with classical electromagnetic theory, but its founders encountered a few stumbling blocks when the theory's logical consequences clashed with their physical intuition. One main concern, presented in a famous 1935 paper by Albert Einstein, Boris Podolsky and Nathan Rosen, was that quantum theory is incomplete and needs to be augmented with hidden variables to capture the real physical situation[2].

The basis of their objection was as follows. According to quantum theory, a pair of quantum objects can be described as though it is a single unit, with measurements on each object returning correlated results even when the two objects are physically far apart. (Such pairs were later termed entangled.) However, in an acceptable theory, each object should be fully describable on its own, and no communication or other physical influences should travel faster than the speed of light; the latter is a principle known as locality. Because quantum theory offers no description for each entangled object independently, Einstein and colleagues concluded that the theory was incomplete.

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Figure 1 | An experimental test with superconducting qubits. This 30-metre cryogenic vacuum system houses two superconducting quantum bits (qubits), connected by a superconducting aluminium waveguide, at temperatures below 50 millikelvin. Storz *et al.*[1] used this set-up to demonstrate a feat known as a 'loophole-free' Bell experiment. In doing so, they developed technologies that push the limits of the superconducting-qubit platform, a promising technology for future quantum computers.

Although the physicists responsible for developing quantum mechanics found the theory deeply disquieting, this same property of entanglement is now viewed as a resource for quantum technologies such as quantum computing. A key point on entanglement's journey from nuisance to resource was to come nearly three decades after Einstein and colleagues' initial objection.

In 1964, John Bell discovered that in any theory of the sort envisaged by Einstein and colleagues — known as a local hidden-variable theory — there is a limit on the extent to which the outcomes of measurements on distant quantum systems can be correlated[3]. Bell captured this limit in a mathematical expression known as Bell's inequality, and also observed that the predictions of quantum mechanics can violate this limit. This means that it is impossible for any augmentation to bring quantum theory in line with a local hidden-variable theory, because there are situations in which the two theories predict different results. A natural next step was to probe those situations in experiments.

To test Bell's inequality, one distributes an entangled pair of objects between two distant measurement stations, conventionally named Alice and Bob, who each choose one of two measurement settings and record one of two possible outcomes. After repeating this process many times, Alice and Bob combine their data to identify the probability of measuring each pair of results given each possible pair of setting choices. These probabilities are the terms of Bell's inequality. Data that lead to a violation of the inequality cannot be described by any local hidden-variable theory. Quantum mechanics makes predictions that violate the inequality.

The first Bell experiments were performed in the 1970s, and most found results that violated the predictions of local hidden-variable theories and agreed with quantum mechanics[4]. This was so surprising at the time that researchers started looking for an experimental error or alternative explanation for the result[5]. Experimental 'loopholes' offer such possible alternative explanations.

Mapping Bell's thought experiment onto a laboratory experiment necessarily involves some assumptions, each of which opens a loophole by which a local hidden-variable theory could explain the outcomes observed. For example, experiments using entangled optical photons often detect only a small set of the photons produced. Researchers can invoke a fair-sampling assumption that supposes the detected subset represents the entire ensemble[6]. However, it is possible to write a local hidden-variable theory that can take advantage of this fair-sampling loophole to achieve a violation of the inequality.

Similarly, a local hidden-variable model that includes hidden communication could explain correlated measurement outcomes — for example, by leveraging what is sometimes called the locality loophole. Noting that communication should not exceed the speed of light, experimentalists can limit any hypothetical communication that such loopholes could exploit by carefully tuning the physical separation and timing of Alice's and Bob's setting choices and measurement activities[7]. Since 2015, experiments addressing all major loopholes simultaneously have been reported in systems based on defects in diamonds[8], optical photons[9,10] and trapped atoms[11]. Storz *et al.* report the first such experiment on a superconducting qubit platform.

The authors' Bell experiment (Fig. 1) includes two functionally identical measurement stations representing Alice and Bob, respectively, each consisting of a single superconducting qubit and a random-number generator used to choose the measurement settings for the Bell test. The qubits are separated by 30 metres and physically connected by an aluminium waveguide structure that carries quantum information in the form of tiny amounts of microwave energy, and is used to establish entanglement between the qubits. The qubits and the entire waveguide structure must be cooled to cryogenic temperatures, with the waveguide below 50 millikelvin and the qubits below 20 millikelvin. Precise synchronization, using an atomic clock, calibrated cable lengths and real-time monitoring, prescribes the timing of each setting choice and measurement activity with subnanosecond precision.

Building a 'loophole-free' Bell experiment is challenging on any platform because the requirements for closing each loophole are often at odds with each other. Addressing the locality loophole requires an experiment with a large footprint and fast, precise timing; closing the fair-sampling loophole generally calls for a smaller experiment so that anything transmitted to distribute entanglement is less susceptible to loss; and acquiring adequate statistics requires that data are produced significantly faster than losses and environmental fluctuations can perturb the experimental system.

Two key technological developments enabled the success of Storz and colleagues' Bell experiment. By achieving a single-qubit readout of around 50 nanoseconds, much faster than the few hundred nanoseconds that define the multi-qubit state-of-the-art systems[12,13], the authors were able to reduce the required qubit separation to around 30 metres. Then, they developed a low-loss cryogenic waveguide of this size and integrated it with the qubits to reach a high-fidelity connected system.

Photon-based implementations typically violate Bell's inequality by a small margin, but with a data-production rate high enough to show a statistically significant violation in a relatively short collection time. Matter-based implementations usually violate the inequality by a larger margin, but have low data-acquisition rates, making it difficult, or at least time consuming, to reach high statistical certainty. Storz and colleagues' set-up violates Bell's inequality by a higher margin than previous photon-based experiments, with a higher rate of data production than that obtained in previous matter-based experiments[8–11].

This Bell experiment sets a record for the longest separation between two entangled superconducting qubits, and is impressive because of its physical size and precision. Although the 50-nanosecond readout demonstrated here cannot readily be applied to multi-qubit quantum computers, it pushes this qubit technology to new limits. Similarly, although the superconducting-waveguide approach does not scale to arbitrary distances, it represents a path towards quantum-information transfer between superconducting-qubit chips, a technology that will be needed in a large-scale quantum computer. With the achievement of this foundational quantum milestone, and the technological advancements that enabled it, Storz *et al.* have expanded the superconducting-qubit toolbox and given further credibility to this promising platform.

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Forum: Genomics

A collective human reference genome

A pangenome is a collection of DNA sequences that reveals genetic variation between individuals. Four scientists discuss the generation of a human pangenome, and what insights can be gained from it. **See p.312, p.325 & p.335**

Arya Massarat & Melissa Gymrek

Describing genetic diversity with graphs

Reference genomes are crucial coordinate systems for genomic analyses. However, the references that scientists currently work from when studying humans (the draft human genome[1] and its complete, gap-free successor[2], dubbed T2T-CHM13) are both based mostly on single individual genomes. A linear genome sequence of this type cannot adequately represent genetic diversity within our species. Instead, such diversity is more accurately described using a graph-based system of branching and merging paths. On page 312, Liao *et al.*[3] describe the first human reference pangenome — a collection of genome sequences compiled into a single data structure.

The use of human reference genomes from single individuals is problematic because it introduces biases in how sequences from other human genomes are interpreted. For instance, sequences from other genomes are first commonly aligned to the reference (read mapping) and then reduced to a set of differences from that reference (variant calling). Both processes might yield different results if a different person's DNA had been used to generate the original reference. This is particularly true for highly diverse and structurally complex regions of the genome. Furthermore, there are hundreds of megabases of DNA that cannot be captured in a reference based on a single genome, because they exist in only a subset of humans[4,5].

A pangenome representing many genomes from different ancestries could overcome these issues. However, constructing a pangenome is a complex task. Breakthroughs in the past decade in long-read sequencing technology and computational methods have now enabled this vision to be realized.

Liao and colleagues first generated 94 genome assemblies from 47 individuals (one for each of the two sets of chromosomes that each individual carries). The individuals represent diverse ancestries from around the globe. The assembled genomes, which were generated using a combination of long-read and other sequencing technologies, are highly accurate and nearly complete, and include 119 million base pairs of sequence not included in the draft human reference genome.

The authors used three graph-building methods to construct pangenomes from these assemblies. One of these methods aligns all sequences simultaneously; the others use one genome as a reference and align each subsequent sequence iteratively. The result is a set of publicly available pangenome graphs, along with a rich ecosystem of open-source tools and standardized file formats that researchers can use in a similar way to a linear reference genome.

Liao *et al.* demonstrated that using their pangenomes for read mapping and variant calling resulted in 34% fewer errors in calling small variants (those shorter than 50 bases) than did using a linear reference. The difference was particularly pronounced in challenging repetitive DNA regions. Impressively, the pangenomes enabled the authors to identify twice as many large genomic alterations, called structural variants, per person than is possible using a linear reference (Fig. 1).

The human pangenome reference represents a milestone in human genetics. However, challenges remain. Alignment of sequences against highly variable repetitive regions in the pangenome could be improved by more-accurate assemblies or new algorithms. More samples from diverse groups are also needed. Finally, widespread adoption of the pangenome by scientists could take time, because new methods supporting pangenome analysis are continually being developed, and scientists will often require training to use them.

Continued improvements in methods for building and using pangenomes will enable researchers to overcome these challenges. Use