cases where gene deletions cause moderate cell loss. The group named their technique CRISPR-lineage tracing at cellular resolution in heterogeneous tissue (CRISPR-LICHT).

The researchers ranked the lineage-barcode depletion of the 173 genes thought to pose a risk of microcephaly, and examined the top 32 genes in further detail. They investigated the role of these genes in regulating cell proliferation by using a mixing strategy, in which they grew organoids from a combination of control cells and cells that had been genetically edited to lack the gene, and analysed the ratio of control to edited cells in the fully grown organoids. Finding significantly reduced numbers of edited cells suggests that deletion of the gene causes reduced proliferation. Of the 32 genes studied, 25 were found to be implicated in cell proliferation.

Finally, Esk *et al.* focused on one particular gene of the set, which encodes immediate early response 3 interacting protein 1 (IER3IP1). When cells were engineered to lack this gene, the resulting organoids were smaller than the controls. Analysis of organoids lacking this gene revealed that it seems to regulate the unfolded protein response – a cellular response to stress in an intracellular organelle called the endoplasmic reticulum that leads to reduced protein synthesis. Treatment of cells with a small molecule called the integrated stress response inhibitor, which restores protein synthesis, led to normal size and organization of neural progenitors in the organoids. These findings are particularly interesting because they tie the stress-induced unfolded protein response, which has previously been associated with Zika virus-related microcephaly[8], to a genetic cause of the disorder. The experiments highlight the enormous potential of CRISPR-LICHT to investigate the mechanisms that underlie neurodevelopmental disorders.

Although Esk and colleagues focused specifically on genes associated with microcephaly, their cost-effective and time-saving method will be widely applicable to other neurodevelopmental disorders. The Developmental Brain Disorder Gene Database (go.nature.com/3mezn8d) lists about 600 genes whose deletion is associated with neurodevelopmental disorders such as autism, schizophrenia and epilepsy. These genes can now be screened by CRISPR-LICHT.

The approach could also be used to study genes that are under- or overexpressed in neurodevelopmental disorders, by adapting it to modify, rather than eliminate, gene expression. Furthermore, the dual-barcoding techniques of CRISPR-LICHT could be used to create and track genetically distinct populations of cells, to model the effects of genetic variations among cells in the developing brain[9]. Finally, the approach could be used to analyse genes associated with cancer.

There are some limitations, however. CRISPR-LICHT is most suited to studies of early development or cell proliferation. The cerebral organoids in the current study were grown for 40 days, corresponding to development of the human brain early in the first trimester, so neurons and glia that develop and mature later were not considered. Using longer differentiation times would increase the turnaround time. Furthermore, current protocols for organoid growth might activate cellular stress pathways, impairing cell-type specification and fidelity[10]. Finally, not all of the cortex is the same, with different regions having cell types and connections that serve different functions. More-precise protocols would be required to model this complexity and regionalization.

Beyond clinical studies, the CRISPR-LICHT platform could be applied to study the genetic changes and mechanisms underlying the evolution of the healthy human brain. Evidence indicates that the expansion and folding of the human cortex depend on human-specific properties of early neuronal development[11–13]. Using brain organoids to screen genes and other DNA elements that are unique to humans, or that exhibit a distinct pattern of activity in humans[14], could be a powerful way of connecting genes to traits in the context of human neural development.

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Information technology

# Artificial intelligence accelerated by light

**Huaqiang Wu & Qionghai Dai**

The explosive growth of artificial intelligence calls for rapidly increasing computing power. Two reported photonic processors could meet these power requirements and revolutionize artificial-intelligence hardware. **See p.44 & p.52**

Artificial intelligence (AI) is transforming various fields, such as clinical diagnosis, autonomous driving and speech translation. However, the quickly increasing volume of data in modern society poses great challenges for the electronic computing hardware used in AI, in terms of both computing speed and power consumption. Such issues have become a major bottleneck for AI. On pages 44 and 52, respectively, Xu *et al.*[1] and Feldmann *et al.*[2] report photonic processors that accelerate AI processing by harnessing the distinctive properties of light. These demonstrations could inspire a renaissance of optical computing.

With the rise of AI, conventional electronic computing approaches are gradually reaching their performance limits and lagging behind the rapid growth of data available for processing. Among the various types of AI, artificial neural networks are widely used for AI tasks because of their excellent performance. These networks perform complex mathematical operations using many layers of interconnected artificial neurons[3]. The fundamental operation that uses most of the computational resources is called matrix–vector multiplication.

Various efforts have been made to design and implement specific electronic computing systems to accelerate processing in artificial neural networks. In particular, considerable success has been achieved using custom chips known as application-specific integrated circuits[4], brain-inspired computing[5] and in-memory computing[6], whereby processing is performed *in situ* with an array of memory devices called memristors.

Electrons are the carriers of information in electronic computing, but photons have long been considered an alternative option. Because the spectrum of light covers a wide range of wavelengths, photons of many different wavelengths can be multiplexed (transmitted in parallel) and modulated (altered in such a way that they can carry information) simultaneously without the optical signals interfering with each other. This propagation of information at the speed of light results in minimal time delays. Moreover, passive transmission (in which no input power is required) aids ultralow power consumption[7], and phase modulation (whereby the quantum-mechanical phases of light waves are varied) enables light to be easily modulated and detected at frequencies greater than 40 gigahertz (ref. 8).

In the past few decades, great success has been attained in optical-fibre communication. However, it remains challenging to use photons for computing, especially at a scale and performance level comparable to those of state-of-the-art electronic processors. This difficulty arises from a lack of suitable parallel-computing mechanisms, materials that permit high-speed nonlinear (complex) responses of artificial neurons and scalable photonic devices for integration into computing hardware.

Fortunately, developments over the past few years in devices called optical frequency combs[9] brought new opportunities for integrated photonic processors. Optical frequency combs are sets of light sources with emission spectra that consist of thousands or millions of sharp spectral lines that are uniformly and closely spaced in frequency. These devices have achieved substantial success in various fields, such as spectroscopy, optical-clock metrology and telecommunication, and were recognized with the 2005 Nobel Prize in Physics. Optical frequency combs can be integrated into a computer chip[9] and used as power-efficient energy sources for optical computing. This system is well suited for data parallelization by wavelength multiplexing.

Xu and colleagues used such a set-up to produce a versatile integrated photonic processor. This device performs a type of matrix–vector multiplication known as a convolution for image-processing applications. The authors implemented an ingenious method to carry out the convolution. They first used chromatic dispersion — whereby the speed of transmitted light depends on its wavelength — to produce different time delays for wavelength-multiplexed optical signals. They then combined these signals along the dimension associated with the wavelength of the light.

By fully exploiting the wide range of photon wavelengths, Xu *et al.* achieved intrinsically parallel computing for different convolution operations. The optical-computing speed was beyond ten trillion operations per second using a single processing core and was limited only by the data throughput. Another welcome feature of this work is that the authors identify the entry point of their photonic convolution processor in practical applications. In particular, they suggest that the processor could be used in a hybrid optical–electronic framework, such as for *in situ* computations during optical-fibre communications.

Feldmann and colleagues independently made an integrated photonic processor that performs a convolution involving optical signals that span two dimensions. The device uses optical frequency combs in an ‘in-memory’ computing architecture that is based on a phase-change material (a material that can switch between an amorphous phase and a crystalline phase). The authors fully parallelized the input data through wavelength multiplexing and conducted analogue matrix–vector multiplication using an array of integrated cells of the phase-change material.

Such a highly parallelized framework can potentially process an entire image in a single step and at high speed. Moreover, in principle, the system can be substantially scaled up using commercial manufacturing procedures and aid *in situ* machine learning in the near future. Because the convolution process involves passive transmission, the calculations of the photonic processing core can, in theory, be performed at the speed of light and with low power consumption. This ability would be extremely valuable for energy-intensive applications, such as cloud computing.

Given the challenges facing conventional electronic computing approaches, it is exciting to see the emergence of integrated photonics as a potential successor to achieve unprecedented performance for future computing architectures. However, building a practical optical computer will require extensive interdisciplinary efforts and collaborations between researchers in materials science, photonics, electronics and so on. Although the reported photonic processors have high computing power per unit area and potential scalability, the all-optical computing scale (the number of optical artificial neurons) remains small. Moreover, the energy efficiency is limited by the presence of computing elements that inherently absorb light and because electrical and optical signals frequently need to be interconverted.

Another avenue of research is the development of advanced nonlinear integrated photonic computing architectures, rather than one- or two-dimensional linear convolutions. By integrating electronic circuits and thousands or millions of photonic processors into a suitable architecture, a hybrid optical–electronic framework that takes advantage of both photonic and electronic processors could revolutionize AI hardware in the near future. Such hardware would have important applications in areas such as communication, data-centre operation and cloud computing.

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Epidemiology

# Big data and simple models to track COVID-19

**Kevin C. Ma & Marc Lipsitch**

Understanding the dynamics of SARS-CoV-2 infections could help to limit viral spread. Analysing mobile-phone data to track human contacts at different city venues offers a way to model infection risks and explain infection disparities. **See p.82**

Behind the highly politicized disagreements over COVID-19 control measures lies a widely shared desire to return economic and social life to sustainable levels as soon and for as long as possible, while preserving health-care systems and minimizing severe illness and death. The main arguments are about the extent to which these goals are mutually reinforcing, and whether there is a trade-off between greater viral transmission and increased social and economic activity. The difficulty in identifying control measures that are both effective and minimally disruptive motivates the search for new approaches to modelling