(exomes) and a burden analysis aimed at prioritizing genes with an excess of variants in cases over controls. The authors focused on three different models for selecting rare variants from the discovery set of 2843 ALS cases and 4310 controls: investigating all nonsynonymous coding variants (when a nucleotide is substituted, thereby producing a different amino acid) and canonical splice variants; looking at nonsynonymous variants that are predicted to be damaging variants; and assessing loss-of-function variants. On the basis of these analyses, 51 genes were taken forward to a replication effort in an additional set of 1318 ALS cases and 2371 controls.

Although an attempt was made to exclude ALS cases with known mutations, it is notable that the top hit in the discovery effort was *SOD1*, a gene encoding superoxide dismutase 1, which is known to contain mutations that cause ALS. Other genes previously associated with ALS were also associated with disease in the analysis, including *TAR DNA BINDING PROTEIN* (*TARDBP*), *OPTINEURIN* (*OPTN*), *VALOSIN CONTAINING PROTEIN* (*VCP*), and *SPASTIC PARAPLEGIA* (*SPG11*).

Cirulli *et al.* performed a large number of analyses and identified a number of interesting genes potentially involved in risk for ALS. However, the most immediately important and compelling finding is the identification of a new association between ALS and variants in *TBK1*, which encodes a noncanonical IκB kinase family member, TANK-binding kinase 1. The authors report an overall excess of rare *TBK1* variants in cases under the "dominant not benign" model (dominant inherited variants that are predicted to be damaging to protein function), with a 0.19% allele frequency in controls versus 1.1% in cases (combined discovery and replication P value = 3.63×10^{-11}). Although these data intuitively suggest that *TBK1* variants play a role in ~0.9% of the ALS cases examined in the study, it is important to recognize that this does not suggest that *TBK1* mutation is sufficient to cause disease, nor does it explain the cause of 0.9% of ALS cases. A great deal of additional work is required to establish whether disease-linked variants in this gene are risk variants, or causal mutations, or both (*2*).

From a functional perspective, the linkage of *TBK1* to ALS is interesting, as it highlights the importance of autophagy and degradation of ubiquitinated proteins in motor neuron degeneration. *TBK1* phosphorylates the proteins encoded by genes previously linked to ALS, *OPTN* and *SEQUESTOSOME 1* (*SQSTM1*). Phosphorylation by Tbk1 enhances the ability of these proteins to shepherd ubiquitinated proteins to autophagosomes for destruction. Vcp and ubiquilin 2 (Ubqln2), also encoded by ALS-linked genes, are involved in later stages of the same cellular pathway, reinforcing the long-held view that ubiquitin-proteasome and autophagy pathways are central to ALS pathogenesis.

The genetics field has changed perhaps more than any other scientific discipline over the past two decades. This transformation has been focused not only on methodology, but also on a more fundamental shift in the way gene hunting is executed. Traditionally a highly competitive field, gene hunting has evolved into a collaborative endeavor in which consortia and open data sharing are central tenets. The type of collaboration typified by Cirulli *et al.* has become a requirement for success. Other examples include large collaborative efforts in Parkinson's disease and Alzheimer's disease (*3*, *4*). Another key to the success of Cirulli *et al.* was their access to publicly available data. Reference data from the Exome Aggregation Consortium (*5*) and the 1000 Genomes Project (*6*) were key steps in their filtering approach. The availability of such control and population sequence data is an essential resource for progress in disease research, and one that promotes efficiency and collaboration.

"The study...marks an early success in...the application of exome sequencing... to identify genetic factors involved in complex disease."

As Cirulli *et al.* rightly point out, much remains to be done to more fully understand the genetics of ALS (see the figure). Their work opens at least one new avenue into the investigation of molecular pathogenesis of disease, linking the protein product of *TBK1* with known ALS proteins. It is likely that their genetic data will also serve as the foundation for further gene discovery in ALS. Given this, it is particularly laudable that the authors have made individual-level exome sequence data rapidly available to the broader scientific community. ■

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REFERENCES

1. E. T. Cirulli *et al.*, *Science* **347**, 1436 (2015).
2. A. Singleton, J. Hardy, *Hum. Mol. Genet.* **20**, R158 (2011).
3. M. A. Nalls *et al.*, *Nat. Genet.* **46**, 989 (2014).
4. J. C. Lambert *et al.*, *Nat. Genet.* **45**, 1452 (2013).
5. exac.broadinstitute.org
6. www.1000genomes.org
7. A. E. Renton, A. Chiò, B. J. Traynor, *Nat. Neurosci.* **17**, 17 (2014).

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APPLIED OPTICS

Sorting out light

Controlled interference can separate overlapping light beams for device functionality

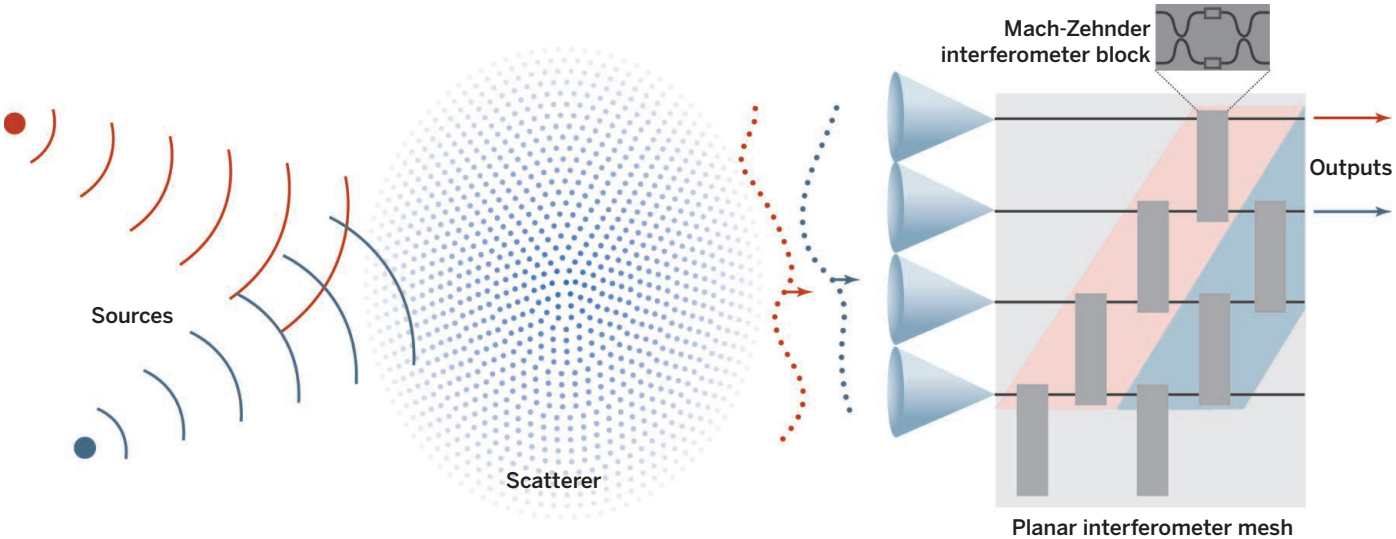
By **David A. B. Miller**

When light beams become mixed up, can we sort them out again? Some cases are easy. The light from two flashlights on the other side of a room overlaps when it reaches us, but the lens in our eye separates them again as it constructs an image. By turning the flashlights on and off, we could also communicate two independent, spatial channels of information to different detectors at the back of our eyes.

But light is readily scrambled by anything more complicated than clear air. Trying to image through a strong scatterer, such as biological tissue, rapidly becomes impossible with increasing sample thickness. Even in the near-perfect glass fibers of optical communications, the slightest bend in the fiber can mix the light beams.

Mathematically, interference of light waves just involves adding and subtracting numbers (which is a linear process), so we can exploit the matrices of linear algebra. With effort, we can measure the optical system's matrix (*1*) and then calculate the inverse matrix that would mathematically undo the mixing. At least, we can do so in principle. However, we did not know how to implement such a (inverse) matrix as a lossless optical component. We did not even know if we could make an arbitrary linear optical device. Now, however, different mathematical approaches (*2*–*6*), together with modern microfabrication, may offer a solution. The optics may even solve the problem itself, thereby avoiding the need for any calculations (*5*, *6*).

Historically, optical components were simple objects, like lenses and mirrors. Now, the lithography developed for electronics offers more sophisticated possibilities. Silicon photonics (*7*) and other integrated approaches enable highly functional, complex (*8*) waveguide circuits near the top of a plane surface. Subwavelength patterning enables novel, nanophotonic structures, including photonic crystals,



Disentangling light beams. Light from two sources is mixed and distorted by the scatterer but sorted out by the mesh. The scattered light is focused into waveguides in the interferometer mesh. Progressively adjusting the interferometers in the "red" row to maximize the "red" output separates the "red" power to the upper output. A similar algorithm on the "blue" row then separates the "blue" power to the lower output. Although shown as "red" and "blue," the sources can be the same color or wavelength.

waveguides, and resonators. Expanding beyond regular structures offers an even wider variety (*2*–*5*).

We already use lithography to make diffractive optical elements; in such elements, light travels through a thin sheet from one side to the other (or possibly reflects off it). Metasurfaces are extending these possibilities (*9*). By itself, such an approach cannot implement arbitrary linear optics. A fully arbitrary device (*5*) requires that every distinct element or pixel in the output light can be formed from an arbitrary combination of every distinct input pixel, not just by transmission or reflection from the same input pixel.

If the light travels inside the sheet, in waveguides or other complex structures, then light from every input element can possibly interfere to form each output. This multiple scattering makes device design hard, both mathematically speaking and from a fabrication point of view. Modern robust optimization algorithms allow efficient blind global optimization, however. Various compact nanophotonic devices have now been designed (*2*–*4*), for example, efficiently converting one set of input beams (or "modes") to another set of output beams (*2*, *3*).

Another planar approach uses meshes of interfering waveguides (*5*, *10*) (see the figure). The optical properties of the mesh can be programmed through fine adjustments of the lengths or phase shifts of waveguide links. The mesh settings have been known for one class of matrices (unitary transformations) for some time. Now, we know that an extended form of mesh can implement any matrix, finally proving that any linear optical component is possible in principle (*5*).

A key to this proof is that we can always perform a singular value decomposition (SVD) of such a matrix (*5*). The SVD has a simple physical interpretation: For any linear optical device or scatterer, there is a specific set of input beams or modes that couple, one by one, to a specific set of output beams or modes. These input/output pairs or communications modes (*5*) completely describe the device and give independent optical channels through it. The proof is also the design method, mapping the form of the SVD directly into the optics. This SVD approach has another benefit; it allows a progressive, even self-configuring, algorithm (*5*). We can then progressively train an extended version of the simple device shown in the figure, using the communications modes themselves, with no calculations.

There are still many challenges. We are only at the beginning in being able to fabricate actual optical structures and devices based on the optimization or self-configuring algorithms. The complexity of optical systems we can tackle this way will be limited. Imaging even a moderate number of pixels through a strong scatterer will remain very challenging. Not all the problems of using multiple mode fibers for communications can easily be solved in the optical domain; time delays between channels in long fibers may necessitate electronic information storage and calculations (*11*).

Beyond telecommunications or imaging, there are many other potential applications for bespoke linear optical elements. We need sophisticated optical networks for quantum information processing (*10*) and for sensor and signal processing generally. Linear optical processors could avoid the power dissipation of electronics. Complex optics could secure signals against decoding (*12*). Real-time self-configuration could allow automatic beam coupling, optical power combining, tracking of moving sources, and alignment or stabilization of complex optical systems (*5*). Extensions of these approaches could find the best channels through an optical system (*6*). The combination of micro- and nanofabrication, planar optical technologies, advanced robust optimization algorithms, and new self-configuring networks may both generate the new optical results we want and eliminate the ones we would rather avoid. ■

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REFERENCES AND NOTES

1. A. P. Mosk, A. Lagendijk, G. Lerosey, M. Fink, *Nat. Photonics* **6**, 283 (2012).
2. V. Liu, D. A. B. Miller, S. H. Fan, *Proc. IEEE* **101**, 484 (2013).
3. J. Lu, J. Vučković, *Opt. Express* **21**, 13351 (2013).
4. C. M. Lalau-Keraly, S. Bhargava, O. D. Miller, E. Yablonovitch, *Opt. Express* **21**, 21693 (2013).
5. D. A. B. Miller, *Photonics Res.* **1**, 1 (2013).
6. D. A. B. Miller, *J. Lightwave Technol.* **31**, 3987 (2013).
7. W. Bogaerts, M. Fiers, P. Dumon, *IEEE J. Sel. Top. Quantum Electron.* **20**, 1 (2014).
8. J. Sun, E. Timurdogan, A. Yaacobi, E. S. Hosseini, M. R. Watts, *Nature* **493**, 195 (2013).
9. N. Yu, F. Capasso, *Nat. Mater.* **13**, 139 (2014).
10. P. J. Shadbolt *et al.*, *Nat. Photonics* **6**, 45 (2012).
11. R. Ryf *et al.*, *J. Lightwave Technol.* **30**, 521 (2012).
12. S. A. Goorden, M. Horstmann, A. P. Mosk, B. Škorić, P. W. H. Pinkse, *Optica* **1**, 421 (2014).

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ILLUSTRATION: C. SMITH/*SCIENCE*

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