50 Years Ago

An Introduction to the Logic of the Sciences. By R. Harré — This is a very welcome book. It should be said at the outset that the author's intention to write largely for undergraduates in science may prove a little on the modest side, since many students working for higher degrees would probably produce substantially better theses if they could find time to read what Dr. Harré has to relate … The grand point is that — from the aspect of discovery — disciplined insight came first, and the application of mathematical analysis afterwards. Essential as the latter is, momentous advances usually begin with remarkably simple premises. Incidentally, Max Planck is known to have fought long and hard in his mind against the consequences of his own quantum concept. The statistical and indiscriminate nature of much of modern physics was not to his liking. But that is the penalty of greatness. Questions like these are ably handled by Dr. Harré, and the moral is driven home.
From *Nature* 8 October 1960

100 Years Ago

Beet Sugar Making and its Chemical Control. By Y. Nikaido — In principle, the production of sugar from beetroots is a simple matter. The sugar and other soluble bodies are extracted from the sliced roots by diffusion in water; the juice thus obtained is purified from acids and other objectionable matter by "defecation" with lime, and after the excess of lime has been removed by treatment with carbonic acid, the liquor is concentrated by evaporation until the sugar crystallises out. Whilst, however, there is nothing complicated about the principle, successful and profitable production depends upon close attention to a number of points in respect of which the chemist's help is needed.
From *Nature* 6 October 1910

VISION

Neurons show their true colours

How do we tell red from green? Work on the primate retina shows how neural circuitry combines signals from individual cone photoreceptor cells to provide the basic building blocks for colour vision. SEE ARTICLE P.673

JONATHAN B. DEMB & DAVID H. BRAINARD

The processing of visual information begins in the retina, where specialized neurons called photoreceptors absorb light and stimulate multiple neural circuits. Each circuit generates specific patterns of electrical activity and converges on one of about 20 types of retinal ganglion cell. These cells' axons — the optic nerve fibres — then convey signals to various brain targets. For colour vision, specific retinal circuits compare the activity levels of different types of cone photoreceptor cells that have different spectral sensitivities[1]. On page 673 of this issue, Field *et al.*[2] describe simultaneous recordings from hundreds of ganglion cells, and a new method to map the inputs that these cells receive from individual cones. The results provide insight into the initial stages of colour vision.

Old World primates, including humans, have three types of cone photoreceptors that are maximally sensitive to long (L), middle (M) or short (S) wavelengths of light. In isolation, however, each cone is colour-blind because its activity depends on both the wavelength and intensity of incident light[1]. For example, an M cone's activity would be the same for a dim green light and a bright red light. Neural circuits derive a colour signal by comparing the activity of different cone types — cone opponency. In primate retinas, there are two broad classes of opponency: S–(L+M) opponency contrasts the activity of S cones with the combined activity of L and M cones, whereas L–M opponency contrasts the activity of L and M cones.

Primate cones are arranged in a mosaic, presenting several challenges to implementing cone opponency (Box 1). First, only a single cone exists at each location in the mosaic, so comparing cone signals confounds spatial and spectral information. Second, S cones are sparse, limiting the spatial resolution of S–(L+M) opponency. Third, the M/L cone arrangement is random or nearly random, leading to 'clumps' of either cell type[2,3]. This limits the spatial resolution of L–M opponent signals. For example, L–M resolution must be coarser at the centre of a clump of L cones than in a region where L and M cones alternate.

S–(L+M) opponency is an ancient and well-developed subsystem of colour vision. The genes encoding the S and M/L cone opsins — proteins that determine spectral sensitivity — diverged more than 500 million years ago[4]. Moreover, the primate retina contains specialized ganglion cells for computing S–(L+M) opponent signals. The small bistratified ganglion cells, for example, receive excitatory inputs from S cones through S-cone bipolar cells, and (L+M) cone signals oppose the S-cone signals by means of two distinct retinal pathways[5]. Similar cone opponency is mediated by ganglion cells in other mammals[6,7].

As for L–M opponency, this depends on a third opsin that arose in Old World primates less than 40 million years ago[4]. The neural mechanisms underlying L–M opponency have remained elusive. It could be that a specialized ganglion-cell type analogous to the small bistratified cells collects pure antagonistic signals from L and M cones[8]. So far, however, there has been no definitive identification of such cells.

Alternatively, L–M opponency might arise in other cells that existed before the emergence of the third cone opsin. A favourite candidate is the midget ganglion cell, named for its small size in the fovea — the central part of the retina[1]. In the fovea, each of these cells connects through a midget bipolar cell to a single cone, and thus receives an excitatory 'centre' signal that is selective for L or M. The centre signal is opposed by a 'surround' signal that is driven by the surrounding cones. Consequently, even if the surround draws randomly on L and M cones, most foveal midgets will exhibit a degree of L–M opponency because the centre signal is always pure[9] (Box 1).

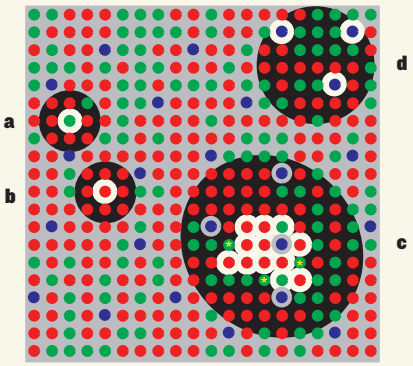
Each ganglion-cell type tiles the retina completely, but is larger in the retinal periphery than in the fovea[1]. The centre signals of the larger midget cells in the periphery therefore connect to a dozen or more cones, and analysis of these connections should provide information about the M/L selectivity of peripheral midget cells. The selective-wiring hypothesis predicts selective connections between each midget cell and either M or L cones; the random-wiring hypothesis, by contrast, predicts random connections[1]. Evidence has been reported in favour of both hypotheses[10,11], making it difficult to rule either out definitively. To date, one roadblock has been that inputs to

BOX 1

Cone opponency in the primate retina

A schematic representation of the mosaic arrangement of cones in the monkey retina that are sensitive to long (L, red), middle (M, green) and short (S, blue) wavelengths of light. S cones are rare, constituting 5–10% of the mosaic, and L cones outnumber M cones by about 2 to 1. L and M cones are arranged near randomly. For simplicity, the cone mosaic is shown as rectangular in arrangement. The actual mosaics are more hexagonal and also less regular[3]: in the central all-cone fovea, cones are tightly packed, whereas in the retinal periphery they are separated by the more numerous rod photoreceptors, which are used for seeing in dim light.

a, In the central fovea, a midget ganglion cell combines an excitatory centre-region signal driven by a single cone — outlined in white — with an opposing signal from the surrounding region driven by surrounding cones (outlined in black). This cell would have M–L opponency.



b, A midget ganglion cell that aligns with a clump of L cones, however, would lack opponency, because the centre and surround are driven by the same class of cones.

c, In contrast to foveal midget ganglion cells, a peripheral midget cell may receive excitatory input from a dozen cones. There is a bias, measurable across the population of cells, in which the centre region of the receptive field is wired to favour one cone type, tending towards cone purity. In this case, for example, the midget cell avoids some M cones near those that comprise the centre (marked with a yellow asterisk) in favour of the L cones that make up the majority. This cell will have L–M opponency. In this example, the S cones are skipped, but a subgroup of midget cells is connected with S cones[2].

d, For S−(L+M) opponency, a small bistratified ganglion cell receives an S-cone input that is opposed by M/L cone inputs. Because of the irregular layout of S cones and other features of the underlying neural circuitry, these cells lack the canonical centre–surround structure found in many other ganglion-cell types, including midget cells[1,5,8]. **J.B.D. & D.H.B.**

ganglion cells could not be characterized on a cone-by-cone basis.

In a technical tour de force, Field *et al.*[2] used a multi-electrode array to generate very high-resolution centre–surround receptive-field maps simultaneously from hundreds of macaque retinal ganglion cells *in vitro*. The array has hundreds of metal electrodes that detect the rates of action potentials that normally travel down the optic nerve. With recordings made in as little as one hour, the authors could not only measure inputs to ganglion-cell centres and surrounds at the resolution of individual cones, but also determine the type of each cone with high accuracy. Their data show how individual peripheral midget cells draw on cones of different types.

Across the midget-cell population, Field and co-workers observed a continuum of cone selectivity in the cell centres, ranging from pure M or L input to a random mix of the two. An elegant re-sampling analysis[2] showed that although the random-wiring hypothesis provides a first-order account of the chromatic properties of the midget-cell population[11], it fails to account for these properties in detail. That is, if the midget centres drew randomly on cones — irrespective of the cone type — there would be less opponency in the population as a whole than is actually observed. Instead, selectivity in the weighting of cone inputs biases the centres towards M or L purity. This bias enhances L–M opponency across the midget-cell population, and could thereby improve the quality of red–green colour vision in the retinal periphery.

Of the questions that Field and colleagues' study highlights, two are particularly fascinating. First, how does the observed specificity of cone inputs come about? Expression by gene therapy of a third cone opsin in the retinas of adult New World monkeys that had been red–green colour-blind since birth[12] allowed them to distinguish between new colours. Theoretically, these new abilities could be mediated by random wiring into the cone mosaic, which would be sufficient to generate some degree of cone opponency[9]. But it would be interesting to determine this experimentally. This could be done using Field and colleagues' method for mapping the receptive fields of ganglion cells at individual-cone resolution. If these cells show random wiring following gene therapy in adulthood, similar receptive-field mapping experiments could be performed in the subset of female New World monkeys born with the three cone types[13,14], to determine whether the plasticity required for cone-selective wiring occurs during development. If biased cone connectivity never occurs in New World monkeys, it would suggest that cone-selective wiring developed in Old World primates on an evolutionary timescale.

And how crucial is the observed degree of selective cone input for red–green colour vision? Psychophysical measurements[8,15] have shown that red–green sensitivity degrades in the retinal periphery, and that its spatial resolution is coarse. The question is whether this performance is better than would be expected from random wiring alone[9]. Field and co-workers' physiological measurements[2], which describe the properties of the entire population of midget cells in a peripheral region of the retina, may help us to more sharply analyse such psychophysical data to understand the precise functional implications of the bias towards selective wiring. ■

Jonathan B. Demb *is in the Department of Ophthalmology and Visual Sciences, and the Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, Michigan 48105, USA.*
David H. Brainard *is in the Department of Psychology, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.*
e-mails: jdemb@umich.edu; brainard@psych.upenn.edu

1. Dacey, D. M. *Annu. Rev. Neurosci.* **23,** 743–775 (2000).
2. Field, G. D. *et al. Nature* **467,** 673–677 (2010).
3. Hofer, H., Carroll, J., Neitz, J., Neitz, M. & Williams, D. R. *J. Neurosci.* **25,** 9669–9679 (2005).
4. Nathans, J., Thomas, D. & Hogness, D. S. *Science* **232,** 193–202 (1986).
5. Crook, J. D. *et al. J. Neurosci.* **29,** 8372–8387 (2009).
6. Yin, L., Smith, R. G., Sterling, P. & Brainard, D. H. *J. Neurosci.* **29,** 2706–2724 (2009).
7. Li, W. & DeVries, S. H. *Nature Neurosci.* **9,** 669–675 (2006).
8. Calkins, D. J. & Sterling, P. *Neuron* **24,** 313–321 (1999).
9. Lennie, P., Haake, P. W. & Williams, D. R. in *Computational Models of Visual Processing* (eds Landy, M. S. & Movshon, J. A.) 71–82 (MIT Press, 1991).
10. Martin, P. R. *et al. Nature* **410,** 933–936 (2001).
11. Diller, L. *et al. J. Neurosci.* **24,** 1079–1088 (2004).
12. Mancuso, K. *et al. Nature* **461,** 784–787 (2009).
13. Jacobs, G. H. *Phil. Trans. R. Soc. B* **364,** 2957–2967 (2009).
14. Blessing, E. M. *et al. J. Physiol. (Lond.)* **557,** 229–245 (2004).
15. Hansen, T., Pracejus, L. & Gegenfurtner, K. R. *J. Vis.* **9**(4), article 26 (2009).