studies [11,13–16] by exploring complex aspects of shape discrimination, its context dependence, and the underlying strategies that rats follow. Their work also provides an important step forward toward the goal of linking specific cell types and circuits with higher order visual perceptions. One can now imagine combining the psychophysics paradigm described here with a head-fixed or mobile imaging protocol [16–18], to directly monitor and control [4,5] the activity of the brain circuits hypothesized to mediate shape recognition. These are truly exciting times for studying visual perception in rodents. As Vermaerke and Op de Beeck [1] rigorously show, rodents not only see, they can also perform discrimination tasks that parallel the visual challenges humans face every day. The general neural circuit mechanisms of shape perception are therefore within reach.

References

1. Vermaercke, B., and Op de Beeck, H. (2012). A multivariate approach reveals the behavioral templates underlying visual discrimination in rats. Curr. Biol. *22*, 50–55.
2. Werner, J.S., and Chalupa, L.M. (2004). The Visual Neurosciences (Cambridge: MIT Press).
3. Newsome, W.T., Britten, K.H., and Movshon, J.A. (1989). Neuronal correlates of a perceptual decision. Nature *341*, 52–54.
4. Fenno, L., Yizhar, O., and Deisseroth, K. (2011). The development and application of optogenetics. Annu. Rev. Neurosci. *34*, 389–412.
5. Luo, L., Callaway, E.M., and Svoboda, K. (2008). Genetic dissection of neural circuits. Neuron *57*, 634–660.
6. Huberman, A.D., and Niell, C.M. (2011). What can mice tell us about how vision works? Trends Neurosci. *34*, 464–473.
7. Wong, A.A., and Brown, R.E. (2006). Visual detection, pattern discrimination and visual acuity in 14 strains of mice. Genes Brain Behav. *5*, 389–403.
8. Krahe, T.E., El-Danaf, R.N., Dilger, E.K., Henderson, S.H., and Guido, W. (2011). Morphologically distinct classes of relay cells exhibit regional preferences in the dorsal lateral geniculate nucleus of the mouse. J. Neurosci. *31*, 17437–17448.
9. Gao, E., DeAngelis, G.C., and Burkhalter, A. (2010). Parallel input channels to mouse primary visual cortex. J. Neurosci. *30*, 5912–5926.
10. Niell, C.M., and Stryker, M.P. (2008). Highly selective receptive fields in mouse visual cortex. J. Neurosci. *28*, 7520–7536.
11. Zoccolan, D., Oertelt, N., DiCarlo, J.J., and Cox, D.D. (2009). A rodent model for the study of invariant visual object recognition. Proc. Natl. Acad. Sci. USA *106*, 8748–8753.
12. Geisler, W.S. (2011). Contributions of ideal observer theory to vision research. Vision Res. *51*, 771–781.
13. Douglas, R.M., Neve, A., Quittenbaum, J.P., Alam, N.M., and Prusky, G.T. (2006). Perception of visual motion coherence by rats and mice. Vision Res. *46*, 2842–2847.
14. Meier, P., and Reinagel, P. (2011). Rat performance on visual detection task modeled with divisive normalization and adaptive decision thresholds. J. Vis. *11*, 10.1167/11.9.1.
15. Busse, L., Ayaz, A., Dhruv, N.T., Katzner, S., Saleem, A.B., Scholvinck, M.L., Zaharia, A.D., and Carandini, M. (2011). The detection of visual contrast in the behaving mouse. J. Neurosci. *31*, 11351–11361.
16. Andermann, M.L., Kerlin, A.M., and Reid, R.C. (2010). Chronic cellular imaging of mouse visual cortex during operant behavior and passive viewing. Front. Cell Neurosci. *4* 10.3389/fncel.2010.00003.
17. Rochefort, N.L., Narushima, M., Grienberger, C., Marandi, N., Hill, D.N., and Konnerth, A. (2011). Development of direction selectivity in mouse cortical neurons. Neuron *71*, 425–432.
18. Dombeck, D.A., Khabbaz, A.N., Collman, F., Adelman, T.L., and Tank, D.W. (2007). Imaging large-scale neural activity with cellular resolution in awake, mobile mice. Neuron *56*, 43–57.

Department of Neurosciences, Neurobiology Section in the Division of Biology and the Department of Ophthalmology at the University of California, San Diego, CA 92093, USA.
E-mail: ahuberman@ucsd.edu

DOI: 10.1016/j.cub.2011.11.047

Human Microbiome: A Genetic Bazaar for Microbes?

A recent study suggests that lateral gene transfer has been particularly intense among human-associated microbes. What can this tell us about our relationship with our internal microbial world?

Morgan G.I. Langille, Conor J. Meehan, and Robert G. Beiko

The transfer of genetic material between organisms, independent of a reproductive cycle, is referred to as lateral gene transfer or LGT. While no class of genes is unaffected by the phenomenon, LGT appears more frequently to involve genes that directly affect the adaptation of prokaryotes to their environment. For example, investigation of gene origins in *Legionella pneumophila* found that several genes of eukaryotic origin were involved in increased virulence in this pathogen [1]. This is a strong indicator that long-distance lateral gene transfer events can have a significant impact on the virulence of a bacterium, including species important to human health. If LGT is a major avenue of microbial adaptation, then microbes may be able to adapt very quickly to new anthropogenic habitats in unpredictable ways. In a recent paper, Smillie and colleagues [2] comprehensively analysed over 2000 prokaryotic genomes to examine the role of LGT in a range of habitats, including the human body; their most striking finding was that pairs of human-associated species have an implied rate of LGT that is 25 times higher than pairs living together in other environments.

A successful LGT event proceeds in three critical steps: transfer of genetic material from a donor to a recipient organism; integration of the transferred DNA into the recipient genome; and fixation of some or all of the transferred material due to selection or drift [3]. LGT between closely related organisms is most likely to be successful when there is a compatibility of exchange mechanisms (such as plasmids or transducing phage) and gene expression mechanisms, and the ready integration of acquired material via homologous recombination. However, genes have been shared between organisms from different phyla and domains of life, indicating that phylogenetic or taxonomic distance is not an absolute barrier to transfer [4–6]. An important question, difficult to answer by bioinformatics alone, is whether a putatively transferred gene is actually used by the recipient lineage, or is undergoing a process of mutational decay that will ultimately result in loss from the genome [7]. It is possible that many inferred LGT events are of no benefit to the organism, and merely reflect a “churn” of DNA into and out of the genome [8].

Robust identification of LGT events is challenging, and many phylogenetic and non-phylogenetic approaches have been developed [9,10]. Smillie *et al.* [2] utilised a public database of 2,235 completed bacterial and archaeal genomes, along with their associated

habitat information, to identify remarkably high levels of LGT among human-associated microbes. The authors took a conservative approach, identifying pairs of genomes that have stretches of DNA at least 500 nucleotides in length, with overall identity of 99% or greater. This approach will identify only very recent LGT events that are most likely to reflect signals of recent adaptation, and eliminates many of the pitfalls associated with identifying LGT while still allowing solid biological insights into an important subclass of LGT events.

Smillie *et al.* [2] used the almost 17,000 recently transferred genes detected to contrast ecological overlap, phylogenetic similarity, and geographic proximity as potential drivers of LGT. They found that the rate of LGT increases between species within the same body site and with increased phylogenetic proximity, with the most closely related groups (which differ by ~3% in the sequences of their small-subunit RNA genes) having up to 40% of pairs of genomes sharing genes. Inter-site transfer rates, even for closely related organisms or within similar geographical locations, are much lower by comparison, while rates within other, non-human-associated communities still exceed the rates between communities. The key conclusion from this work is that ecology is the main determining factor for levels of gene sharing, rather than phylogeny or geography.

Turning their attention to the different functional classes that were represented by these LGTs, Smillie *et al.* [2] found that 27% of the LGTs were associated with mobile genetic elements such as transposons, phages and plasmids. The remainder encoded other functions, including many predicted proteins of unknown function. The authors chose to focus on an interesting class of genes that seemed to not follow the general trend of increased within-site LGT: antibiotic resistance genes. The highest proportion of antibiotic resistance gene sharing was observed between human, farm, and animal-associated microbes. The authors argue that antibiotic resistance is an exception to the trend because it provides a non-specific selective advantage to species independent of their ecological niche. This viewpoint is consistent with other studies that had previously shown that human [11] and soil-associated microbiomes [12] are reservoirs for antibiotic resistance genes.

By contrast, genes shared within a specific site may likely reflect adaption to a particular habitat or niche. Smillie *et al.* [2] found that distantly related meningitis-associated bacteria have shared genes, such as those encoding adhesins and hemolysins, that are important to establishment and progression of the disease. The authors suggest that this approach could be used to identify other genes that are associated with particular diseases and environments, such as pneumonia, endocarditis, hot springs, and soil. An interesting example of a potential between-habitat LGT is the inferred transfer event from a marine microbe to a type of gut bacterium present only in Japanese individuals [13]. The transferred genes enable the breakdown of a polysaccharide from the familiar nori seaweed used in sushi, allowing the microbiome of these individuals to make use of this energy source.

The findings of Smillie *et al.* [2] suggest that ecology is the dominant driver of LGT and that the human microbiome is particularly suited to exchange of genes. However, many questions remain open. For instance, the high proportion of inferred LGTs that implicate mobile elements or hypothetical proteins underlines the question of what proportion of these LGTs has been beneficial to the recipient organism. Is adaptive evolution via LGT a trait of the human microbiome, or are these organisms just more mechanistically inclined to acquire genetic material from the environment? Also, different environments contain different relative proportions of different major groups of bacteria: for example, phyla Firmicutes (particularly class Clostridia) and Bacteroidetes dominate the human gut, with relatively low proportions of other phyla in healthy individuals [14]. Clostridia are known to be ardent exchangers of genes [15], so is the observed effect mainly a consequence of elevated levels of this class of organisms in the gut relative to other habitats?

This work and its broader context have two important implications. First, the ongoing debate of the nature of the 'Tree of Life' in light of LGT and other forces [16,17] must take into account these findings. A phylo-centric viewpoint, one that focuses on finding the 'true tree' through analysis of a small number of conserved loci, needs to be balanced against an eco-centric viewpoint that considers ecological relatedness as an important shaping factor in evolutionary affinities. Just as ancient transfers appear to have greatly facilitated the evolution of photosynthetic [18], thermophilic [4] and acidophilic [19,20] organisms, so recent events may have remodelled the genomes of human-associated microbes. Second, if the microbes that live inside us constitute a group of individual lineages tightly bound by LGT, how does this impact on our understanding of the role of microbes in health and disease? If traits are readily shared amongst our microbial pathogens, symbionts and passengers, then we need to understand the range of potential changes that can arise due to LGT, and carefully consider the consequences of altering the microbial composition and selective regimes within our own bodies.

References

1. Lurie-Weinberger, M.N., Gomez-Valero, L., Merault, N., Glockner, G., Buchrieser, C., and Gophna, U. (2010). The origins of eukaryotic-like proteins in *Legionella pneumophila*. Int. J. Med. Microbiol. *300*, 470–481.
2. Smillie, C.S., Smith, M.B., Friedman, J., Cordero, O.X., David, L.A., and Alm, E.J. (2011). Ecology drives a global network of gene exchange connecting the human microbiome. Nature *480*, 281–284.
3. Thomas, C.M., and Nielsen, K.M. (2005). Mechanisms of, and barriers to, horizontal gene transfer between bacteria. Nat. Rev. Microbiol. *3*, 711–721.
4. Mazodier, P., and Davies, J. (1991). Gene transfer between distantly related bacteria. Annu. Rev. Genet. *25*, 147–171.
5. Beiko, R.G., Harlow, T.J., and Ragan, M.A. (2005). Highways of gene sharing in prokaryotes. Proc. Natl. Acad. Sci. USA *102*, 14332–14337.
6. Cordero, O.X., and Hogeweg, P. (2009). The impact of long-distance horizontal gene transfer on prokaryotic genome size. Proc. Natl. Acad. Sci. USA *106*, 21748–21753.
7. Hao, W., and Golding, G.B. (2004). Patterns of bacterial gene movement. Mol. Biol. Evol. *21*, 1294–1307.
8. Kurland, C.G., Canback, B., and Berg, O.G. (2003). Horizontal gene transfer: a critical view. Proc. Natl. Acad. Sci. USA *100*, 9658–9662.
9. Ragan, M.A. (2001). On surrogate methods for detecting lateral gene transfer. FEMS Microbiol. Lett. *201*, 187–191.
10. Langille, M.G.I., Hsiao, W.W.L., and Brinkman, F.S.L. (2010). Detecting genomic islands using bioinformatics approaches. Nat. Rev. Micro. *8*, 373–382.
11. Sommer, M.O., Dantas, G., and Church, G.M. (2009). Functional characterization of the antibiotic resistance reservoir in the human microflora. Science *325*, 1128–1131.
12. D'Costa, V.M., McGrann, K.M., Hughes, D.W., and Wright, G.D. (2006). Sampling the antibiotic resistome. Science *311*, 374–377.
13. Hehemann, J., Correc, G., Barbeyron, T., Helbert, W., Czjzek, M., and Michel, G. (2010). Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. Nature *464*, 908–912.

14. Eckburg, P.B., Bik, E.M., Bernstein, C.N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S.R., Nelson, K.E., and Relman, D.A. (2005). Diversity of the human intestinal microbial flora. Science *308*, 1635–1638.
15. Sebaihia, M., Wren, B.W., Mullany, P., Fairweather, N.F., Minton, N., Stabler, R., Thomson, N.R., Roberts, A.P., Cerdeño-Tárraga, A.M., Wang, H., *et al*. (2006). The multidrug-resistant human pathogen *Clostridium difficile* has a highly mobile, mosaic genome. Nat. Genet. *38*, 779–786.
16. Bapteste, E., Boucher, Y., Leigh, J., and Doolittle, W.F. (2004). Phylogenetic reconstruction and lateral gene transfer. Trends Microbiol. *12*, 406–411.
17. Lawrence, J.G., and Hendrickson, H. (2003). Lateral gene transfer: when will adolescence end? Mol. Microbiol. *50*, 739–749.
18. Raymond, J., Zhaxybayeva, O., Gogarten, J.P., Gerdes, S.Y., and Blankenship, R.E. (2002). Whole-genome analysis of photosynthetic prokaryotes. Science *298*, 1616–1620.
19. Beiko, R. (2011). Telling the whole story in a 10,000-genome world. Biol. Direct *6*, 34.
20. Bonnefoy, V., and Holmes, D.S. (2011). Genomic insights into microbial iron oxidation and iron uptake strategies in extremely acidic environments. Environ. Microbiol. 10.1111/j.1462–2920.2011.02626.x.

Faculty of Computer Science, Dalhousie University, 6050 University Avenue PO Box 15000, Halifax, Nova Scotia, Canada, B3H 4R2.
E-mail: beiko@cs.dal.ca

DOI: 10.1016/j.cub.2011.11.023

Binocular Vision: The Eyes Add and Subtract

Our two eyes' views of the outside world are slightly different, providing the basis for stereopsis. A new study has found evidence that the human visual system has separately adaptable channels for adding and subtracting the neural signals from the two eyes, supporting an unconventional view of the initial stages of stereopsis.

Frederick A.A. Kingdom

Two forward looking eyes confer upon their owner stereoscopic, or 'three-dimensional' vision. The two eyes view the world from a slightly different angle, and the resulting small differences between the images in the two eyes is exploited for stereopsis. Figure 1 shows an example stereo-pair — readers who can free-fuse the top two images will see a scene in three-dimensions. Underneath are shown the images produced by adding (left) or subtracting (right) the two stereo-half-images. If there were no difference between the two stereo-halves in the upper figure, the lower right image would be blank, so this image reveals the disparities between the two stereo-halves; it is these disparities that are detected by the brain and used to construct the three-dimensional view. Traditionally it was thought that stereopsis was achieved by combining signals from neurons that simultaneously detected objects in disparate parts of the two eyes' images [1], as illustrated in Figure 2A. An alternative view [2], however, suggests that binocular neurons that encode the sum and the difference between the two stereo-halves, shown in Figure 1, are used for stereopsis; this view is illustrated in Figure 2B. While there has been a history of speculation about the possibility of binocular-summing and binocular-differencing channels in human vision [2–4], an ingenious study by May *et al.* [5] reported in this issue of *Current Biology* has finally produced convincing evidence that such channels exist.

May *et al.* [5] focused on a defining feature of Li and Atick's [2] theory about

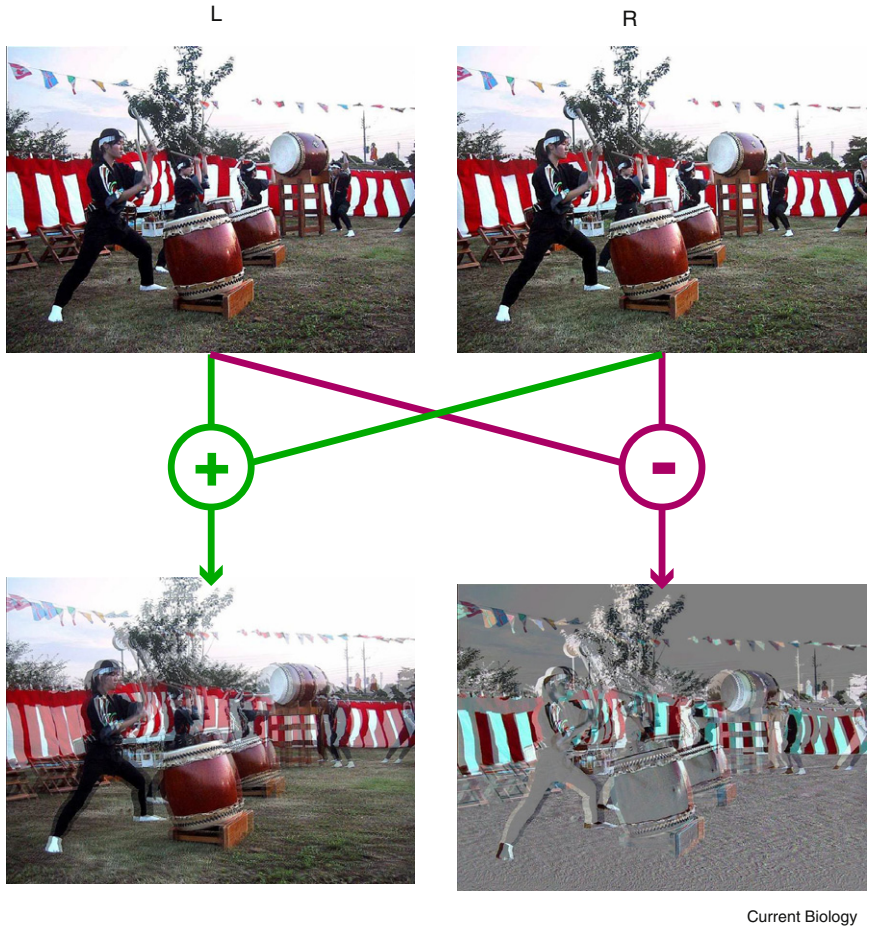

Figure 1. Stereopsis. Fusion of the left (L) and right (R) stereo-half images reveals an image in three-dimensions.

The bottom left image shows the sum and the bottom right image the difference between the two stereo-halves. Although the difference image is weaker than the sum image, it reveals the disparities that are critical for stereopsis.