

In their new study, Bichot *et al.* (1) demonstrate that both sorts of processing occur in area V4 of the visual cortex during a single search task. They recorded neuronal responses from area V4 in the brain of alert macaque monkeys who were searching through displays of colored shapes similar to those shown in the figure. In the first experiment, at the start of a trial, the monkey would be shown a stimulus that cued him to the target color (for example, red) or shape (for example, star). To find this target, the monkey typically made a succession of eye movements that changed the position of the visual stimuli on the retina. During a trial, Bichot *et al.* recorded from a V4 neuron that was sensitive to stimulation in one specific region of the retina (its “receptive field”). Beyond being sensitive to one location in space, a V4 neuron might also have a preferred color and/or shape. Thus, as the monkey moved his eyes around, he presented different stimuli to the receptive field of the neuron under study. If the neuron preferred red stimuli, then, by definition, that neuron responded more vigorously whenever the monkey saw red. Of more interest, on trials when the target color was red, the neuron produced a still larger response. This happened even when the monkey was not about to make a quick eye movement to the target. The red item had not yet become the specific object of attention, but the response of the neuron still received a boost because red was the desired color. Moreover, neurons that preferred the target feature synchronized their activity, perhaps giving them a better chance of activating subsequent postsynaptic neurons.

So much for the parallel enhancement of all items on the basis of a feature like color. What about the selection of specific items? Imagine the situation in which the monkey is searching for a red item, and a red item lies in the receptive field of the studied neuron. We know from previous work (8) that covert attention shifts to an object before it is fixated by the eyes. So Bichot *et al.* went back over their data and sorted the responses into two categories: responses from just before the monkey made an eye movement toward the red item and responses from just before he made an eye movement somewhere else. They found that the neuron responded more strongly just before the eyes fixated on the red item. Thus, it seems that the act of attentional selection that precedes serial fixation also enhanced the response of the neuron. What we have here is attractive evidence at the level of single cells indicating that parallel feature processes are guiding serial selection of plausible targets for further scrutiny.

Understanding how monkeys (and presumably other primates, such as ourselves)

perform search tasks is of more than academic interest. Visual search is a task each of us performs a thousand times a day, from searching for a coffee cup to looking for a face in a crowd. However, some searches are more important than others. As a society, we have created many artificial but critically important search tasks, such as airport baggage screening and routine mammography. Many of these tasks are complicated and currently performed imperfectly. We eagerly await development of new ways to improve human performance on such tasks or the invention of machines that could take over or assist with them. Understanding how biological systems do so well at performing a range of search tasks

should help us to improve the outcome of those artificial search tasks on which we, quite literally, stake our lives.

References

1. N. P. Bichot, A. F. Rossi, R. Desimone, *Science* **308**, 529 (2005).
2. J. Palmer, *Curr. Dir. Psychol. Sci.* **4**, 118 (1995).
3. J. Duncan, G. W. Humphreys, *Psychol. Rev.* **96**, 433 (1989).
4. E. Bricolo, T. Gianesini, A. Fanini, C. Bundesen, L. Chelazzi, *J. Cogn. Neurosci.* **14**, 980 (2002).
5. G. F. Woodman, S. J. Luck, *J. Exp. Psychol. Human Percept. Perform.* **29**, 121 (2003).
6. J. M. Wolfe, *Psychon. Bull. Rev.* **1**, 202 (1994).
7. J. M. Wolfe, *Trends Cogn. Sci.* **7**, 70 (2003).
8. E. Kowler, E. Anderson, B. Doshier, E. Blaser, *Vision Res.* **35**, 1897 (1995).

10.1126/science.1112616

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A Fishing Buddy for Hypothesis Generators

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In the last half of the 20th century, the dominant experimental modality in biology was hypothesis-directed research. Of course, biology has a proud tradition of important insights arising from undirected poking around and following hunches. However, until genomic biology made undirected fishing for information more respectable (1), the most common response to requests for money for such projects was dismissal with the term “fishing expedition.” The study by Sachs *et al.* (2) on page 523 of this issue suggests it may be time to reexamine this prejudice.

In their study, Sachs, Nolan, Lauffenburger, and their co-workers outline what may be a powerful new way to fish. They combine measurements of different signal transduction proteins in large numbers of individual human CD4⁺ T lymphocytes and computational frameworks called Bayesian networks with experimental perturbations that are close to hypothesis-free. These investigators not only regenerated known causal relationships among the signaling proteins but also predicted new connections that they verified by targeted testing. For example, they predicted interpathway cross-talk between the Erk1 and Akt kinases. Their approach suggests a way that “fishing expeditions” and investigator reasoning might supplement one another, generating testable assertions about chains of causation and action in biological systems.

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Consider how biologists identify candidate gene products and suggest how these might act in chains of cause and effect. With “genomic” methods, two grounds for identification correspond to logical fallacies: “guilt by association” (for example, these two proteins touch one another, and might cooperate in the same cellular process) and “post hoc ergo propter hoc” (for example, this gene regulator is expressed before this transcript appears and therefore might regulate production of that transcript) (3). In contemporary biology, such observations are supplemented by additional information including DNA sequences, which can suggest direction of action from the biochemical function of the encoded proteins and similarities to known pathways in other organisms. Such inferences are complemented by experimental methods that more rigorously establish flows of action and consequence. These approaches go back to the work of Ephrussi and Beadle in the 1930s. These experimenters isolated fruit flies with mutations in genes for eye color. They then showed that an eye disk containing the *cinnabar* (*cn*) gene product but lacking the *vermillion* (*vm*) gene product produced a wild-type eye when transplanted into flies that lacked *cinnabar* but contained *vermillion*; they also showed that the converse was not true (4, 5) (see the top figure). This phenomenon, called “epistasis,” established both that *cn* and *vm* act in an eye-color “pathway” and that the wild-type *vm* gene product must act first in order for the wild-type *cn* gene product to exert its effect.