

mechanism. Although the work by Bandell *et al.* represents an analysis of channel mutations more extensive than any previously reported, the nature of the error-prone PCR-based mutagenesis, as pointed out by the authors, precluded the generation of amino acid changes that required two or more changes in a single codon. Thus, it is possible that the identification of additional domains important in activation specifically by menthol or cool will require a different mutagenesis scheme.

The results by Bandell *et al.* are notable, as they suggest that there are differences in the mechanisms of activation of thermoTRPs by chemical versus thermal stimulation. The results also raise the possibility that activation of TRPV1 by heat and pungent chemicals such as capsaicin<sup>5</sup> are also mediated through distinct structural motifs. The same may be true of TRPV3, which is activated by warm temperatures and camphor<sup>10–12</sup>, and TRPA1, which is activated by icilin and naturally occurring pungent compounds<sup>13–15</sup>, and may also be gated by thermal cold<sup>15</sup>, although the response of this latter channel to cold temperatures is controversial<sup>15</sup>.

A key open question concerns the mechanism through which mutations in TRPM8 might affect the response to menthol specifically. As pointed out by the authors, such an effect could occur as a result of mutations that affect ligand binding. However, the domains involved in direct binding of menthol to TRPM8 remain to be determined. Ligand binding could be mediated in part through the S2 domain, as the Y745H mutation induces a specific loss of menthol sen-

sitivity<sup>1</sup>. However, the three key residues in TRPM8 identified by the mutagenesis (Fig. 1) are not sufficient to mediate the menthol response, as two of the same amino acids in wild-type TRPM8 (residues 745 and 1005) are conserved in the most related TRP channel, TRPM2, which is menthol insensitive (Fig. 1b). The proline in TRPM2, which is in the corresponding position of leucine 1009 (Fig. 1b), cannot explain the menthol sensitivity of TRPM8, as introduction of a proline in this position in TRPM8 does not disrupt activation by menthol. Furthermore, substitution of the S2 and TRP domains of TRPM8 into TRPM2 is insufficient to elicit menthol responsiveness in this latter channel. Nevertheless, the analysis of the full set of 15 mutant channels, which display at least a threefold decrease in the menthol-to-cool activation ratio, indicates the importance of hydrophobic residues for activation by menthol. Charged residues, such as arginine seem to be very detrimental for the menthol response, possibly because of the hydrophobic nature of menthol.

The specific role of the highly conserved TRP domain in mediating the menthol response remains to be determined. However, this domain would seem to be very important, as multiple mutations in this region were isolated among the over 4,000 active channels screened. One idea put forth by the authors is that ligand binding, possibly involving the S2 segment, results in conformational changes in the TRP domain, which in turn promotes opening of the channel<sup>1</sup>. Given that the TRP domain is the region most conserved between

TRPC and TRPM channels, the concept that it has a role in facilitating channel opening raises the possibility that this region may be generally important in modulating ligand binding or gating of TRPC and TRPM channels.

Future experiments will be required to determine the minimum sequence requirements for converting a related channel, such as TRPM2, into a menthol/icilin-activated channel. It is also an open question whether it is possible to generate mutations in TRPM8 that greatly and specifically affect activation by thermal cool rather than menthol. Finally, the results of the analysis by Bandell *et al.* raise the exciting possibility that application of similar high-throughput mutagenesis approaches will significantly accelerate the identification of the residues and structural motifs involved in gating of many TRP channels, such as the other thermoTRPs.

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## Measuring the brain's assumptions

Matteo Carandini

**A Bayesian model of visual model perception describes how the brain combines assumption with evidence. A new study in this issue tests and expands the model, building connections between perception, the environment and neural responses.**

Ever wondered why people drive so fast in fog? They might think they are driving slowly. This is because the perception of visual motion is affected by contrast: stimuli of lower contrast generally appear to move

more slowly than stimuli of higher contrast<sup>1,2</sup>. When fog reduces contrast, drivers may think they are maintaining a constant speed when, in fact, they are accelerating<sup>3</sup>.

It might seem puzzling that our otherwise smart visual system would make such a dangerous mistake, but think about the constraints at hand. Visual scenes contain a variety of contrasts, including regions of low or even zero contrast<sup>4</sup>. At high contrast, neural circuits devoted to visual motion may have

little problem reporting the actual stimulus speed. At low contrast, however, these circuits give smaller responses, which are less distinguishable from spontaneous activity; assigning a speed to their output becomes progressively harder and eventually impossible. One solution is for the visual system to make a conservative *a priori* assumption that things are usually not moving, and then to allow this assumption to be overruled by evidence that things are indeed moving. At

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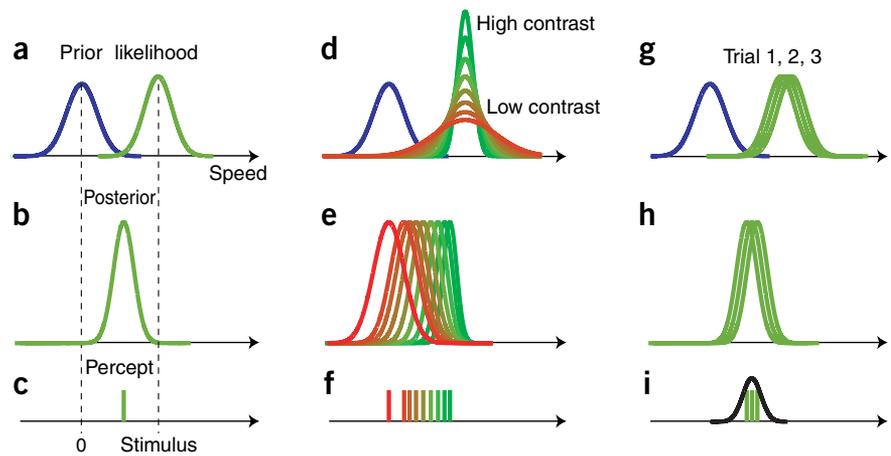
low contrast, such evidence is weak, leaving observers to rely mostly on their assumption and to estimate that speed is slower than it actually is.

An elegant study<sup>5</sup> from Stocker and Simoncelli in this issue provides important evidence in favor of this view by effectively measuring the visual system's assumption that speed at low contrast is zero and by validating a simple Bayesian model for how the brain overrules an assumption based on incoming evidence. This Bayesian model has shown particular promise in describing the perception of visual motion, suggesting a simple unifying explanation for apparently disparate perceptual phenomena<sup>6,7</sup>.

Bayes's simple and well-known equation describes an optimal way to combine a fixed assumption with fresh evidence. A Bayesian observer concerned with speed perception would postulate a prior distribution for stimulus speed based on experience and use the evidence at hand to measure the likelihood of any given stimulus speed (Fig. 1a). The observer would then multiply these two probability distributions to obtain a posterior distribution (Fig. 1b). The prior peaks at zero speed (the conservative assumption), and the likelihood peaks around the actual stimulus speed (if the visual system is doing its job); the Bayesian observer takes as perceived speed an intermediate speed, the speed at the peak of the posterior (Fig. 1c).

The Bayesian model makes quantitative predictions for the apparent slower motion of low-contrast stimuli. Stimulus contrast determines the strength of the signal and therefore determines the width and height of the likelihood (Fig. 1d). With decreasing contrast, the likelihood becomes more shallow and broad, and the posterior becomes more similar to the prior (Fig. 1e). As a result, perceived speed tends to zero (Fig. 1f). This model makes testable predictions for how an observer should rank the speeds of stimuli having different contrast.

In their new study, Stocker and Simoncelli were able to test the Bayesian model much more thoroughly than previous studies<sup>8</sup> because they realized that the model predicts not only how perceived speed should depend on contrast, but also the degree of uncertainty in the observer's judgment. They considered the contribution to this uncertainty of 'measurement noise' arising from physical or neural sources. Physical noise could result from variations in eye position and (at low light intensity) from the variability of photon counts. Neural noise could arise from variability at the various stages of visual processing<sup>9</sup>, particularly because of ongo-



**Figure 1** The Bayesian model of speed perception, and its predictions. (a–c) The Bayesian model of speed perception; (d–f) how the model predicts that perceived speed depends on contrast; (g–i) how the model predicts a distribution of estimated speeds across trials.

ing activity in visual cortex<sup>10</sup>. Measurement noise affects the speed at which the likelihood peaks, making it vary across trials (Fig. 1g). Consequently, in each trial, the posterior is in a somewhat different position (Fig. 1h). The resultant variability in estimated speed across trials defines a probability distribution, whose width reflects the noisiness in the posterior's peak speed (Fig. 1i). Once we know this distribution, we can predict the psychometric function<sup>11</sup> for the probability that an observer will judge a test stimulus to go faster than a reference stimulus. The test speed at which the psychometric function crosses 50% is perceived to be equivalent to the reference speed. The slope of the function is a measure of uncertainty in the observer's judgments<sup>11</sup>.

To test these predictions, the authors collected a large set of speed comparisons. The comparisons involved two stimuli, a reference stimulus of a certain speed and contrast, and a test stimulus of variable speed and contrast<sup>1,2,8</sup>. They fitted the psychometric functions predicted by the model to the data collected at each combination of reference and test, and used these fits to test the model and to estimate the model's parameters.

The success of the fits provides strong support for the Bayesian model. The authors' approach also accounts for aspects of the data that would not have been explained by previous Bayesian models<sup>6,8</sup>. In particular, the new model predicts that the contrast dependence of speed is strong when comparing the test with a reference pattern that moves slowly (for instance, 1 deg per s), but weak when

the reference pattern moves fast (10 deg per s). The data presented clearly support this prediction. Moreover, the results of the model fits revealed some new properties of the prior, which had been thought to be well described by a Gaussian function (as in Fig. 1a). Instead, the authors discovered that the prior has substantially heavier tails (it assigns a higher probability to higher speeds) than had been assumed.

The results of this study also suggest new challenges. Given that the model is so successful in the domain of speed perception, one wonders whether the newly developed methods can be applied to more general questions of motion perception. For example, the Bayesian model also predicts phenomena that involve the direction of two-dimensional motion<sup>6,7</sup>. Can these predictions be made quantitative, and do the data support these predictions? In particular, how could the model be extended to integrate motion signals across space, such as between regions of high and low contrast? Would the assumption that speed does not change abruptly from one location to the next<sup>7</sup> be sufficient to account for perceptual responses? Finally, what is the shape of the cost function used by the observers? The new study<sup>5</sup> assumed that it is equally costly to misperceive something as moving too slowly as it is to misperceive it as moving too fast. Some mistakes (driving in fog comes to mind) may in fact be more costly than others.

At this point, readers might be asking where in the brain, and how, the Bayesian

computation could be performed. These are key questions for which at present we have few answers. We may perhaps agree on how neurons respond to certain stimulus attributes, but we do not really know how the degree of confidence in a given attribute is represented in the brain<sup>12</sup>.

To study Bayesian speed estimation in the primate brain, the first place to look should most likely be visual area MT. Recordings and stimulation indicate that MT is intimately involved in speed discrimination tasks<sup>13</sup>. One should not expect, however, that the contrast dependence of speed perception should be evident in the responses of individual MT neurons. Instead, just as in the retina and in primary visual cortex, decreasing contrast decreases an MT neuron's preferred speed<sup>14</sup>, opposite to the perceptual effect (B. Krekelberg, R.J.A. van Wezel & T.D. Albright. *J. Vis.* **5**, 927a, 2005). It is possible that the contrast dependence of speed perception could result from a simple computation on the population responses, such as a weighted average, where each neuron's contribution is weighted by its preferred speed,

with a bias term favoring responses to zero speed<sup>15</sup>. However, relating these properties of neural responses to concepts of Bayesian estimation remains very much an open question for future research<sup>12</sup>.

For now, Stocker and Simoncelli present tantalizing support for the Bayesian model of motion perception, adding to a growing view that the brain uses Bayesian-like operations to organize actions and form percepts<sup>12</sup>. The key aspect of Bayesian integration that seems to be shared across these actions and percepts is the multiplication of prior knowledge with incoming fresh evidence, a multiplication that also takes into account the uncertainty in the new evidence. By developing a bridge between the Bayesian model and classical concepts of signal detection that are at the heart of psychophysics<sup>11</sup>, this study brings the field forward, allowing future experiments to constrain and test Bayesian theories using hard psychophysical data. Using Bayesian theory to build connections between (i) perceived speed and its uncertainty, (ii) a prior based on ecological constraints and (iii) a likelihood that reflects

cortical noise and contrast sensitivity, the authors bring us a step closer to connecting perception, the environment and neural responses.

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## Go with the flow: signaling from the ventricle directs neuroblast migration

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**Neurons born in the adult subventricular zone migrate a long way to their destination. A new study suggests that signals from the corticospinal fluid, in particular the chemorepellent Slit2, guide adult neuroblast migration.**

Often scientifically neglected areas suddenly return to the spotlight with surprising new functions. The 'boring support cells' radial glia and astroglia have regained attention since the discovery that they act as neural stem

cells during development and adulthood, respectively<sup>1,2</sup>. Radial glial cells during development—and later the astrocytes that act as adult neural stem cells—maintain contact with the brain ventricle cerebrospinal fluid (CSF) via processes that penetrate the ependymal layer, which forms the inner surface of the brain parenchyma. Despite this close contact, little is known about signaling from the CSF into the brain parenchyma. In a recent report in *Science*, Sawamoto and colleagues have unraveled an entirely unexpected role of the CSF in the guidance of newly generated neurons toward the olfactory bulb<sup>3</sup>. However, the new neurons migrate inside the brain parenchyma, so how is this guidance by CSF possible?

Adult neurogenesis takes place in the dentate gyrus and near the ventricle, in the so-called subependymal zone

(SEZ), but there only in a specialized zone lining the lateral wall of the lateral ventricle (**Fig. 1a**, semitransparent cells). No neurogenesis occurs in other ventricle walls. As during development, the birthplace of new neurons is far away from their final position. The neuronal precursors generated by the adult neural stem cells in the SEZ do not contribute to the formation of neurons in the overlying brain region, the striatum, but instead migrate long distances rostrally toward the olfactory bulb (**Fig. 1a**). Only there do they fully differentiate into neurons and integrate into the existing neuronal network. This migration occurs in streams of migrating neuronal precursors (neuroblasts) and is a true long-distance journey that reaches from the back to the very front of the telencephalon. What is it that drives these cells toward the rostral

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