

## Preview

# Image space opens up for visual neuroscience

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How a visual stimulus is perceived depends on the context provided by other stimuli in the scene. Fu et al.<sup>1</sup> combine imaging, modeling, and innovative closed-loop stimulus generation to identify the brain computations that underlie contextual effects in primary visual cortex (V1) neurons.

Perceptual experience is inherently context dependent. Musicians combine sounds, cooks blend flavors, and painters juxtapose colors to create auditory, gustatory, and visual experiences that are profoundly different from the sum of their individual components. In the visual system, this context dependency arises in part from the response properties of neurons in the primary visual cortex (V1). These neurons have a specific area in visual space, called the receptive field, in which the presentation of an image can elicit an increase in activity. Presenting a stimulus in the area beyond the receptive field, called the surround, does not increase neuronal activity above baseline. But when center and surround are jointly stimulated, the resulting response often differs from the response to the center stimulus in isolation.<sup>2</sup> Contextual modulation in the visual cortex defies simple explanations. Seemingly subtle stimulus manipulations elicit effects that range from response suppression to response enhancement. Vision scientists have long been fascinated by this intricacy. Some leveraged center-surround interactions to test hypotheses about the feedforward and feedback flow of signals in cortical circuits,<sup>3</sup> while others used these effects as a critical test bed for stimulus-response models of V1 neurons.<sup>4</sup> Moreover, theorists argued that these effects reveal fundamental coding principles of the brain. They are consistent with the hypotheses that sensory circuits represent information as efficiently as possible<sup>5</sup> and save on the spiking budget by comparing feedforward measurements with feedback predictions.<sup>6</sup> These ideas have become dominant theoretical perspectives on brain function. In other

words, the influence of the surround far surpasses cells in the visual cortex.

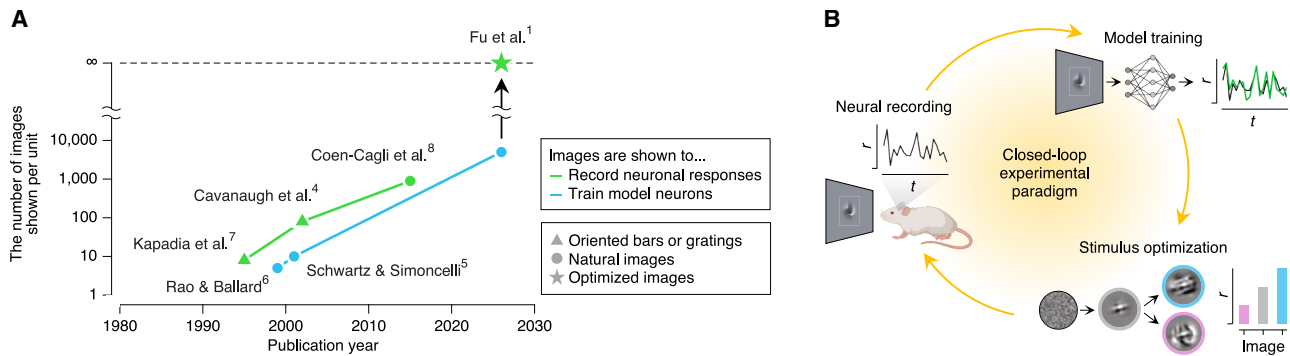
A major challenge in the study of center-surround interaction arises from the vastness of image space. Experimental time is limited, and this characteristic implies that only so many experimental measurements can be completed. How should one select the images to be presented during the experiment? The number of possible images to choose from is overwhelming. Even for relatively small 256-by-256 gray-scale images with an 8-bit luminance scale, the set size ( $256^{(256 \times 256)} \approx 10^{157,826}$ ) vastly exceeds the number of atoms in the universe. Thus far, neuroscientists have adopted two approaches. One is focused on the functional properties of the neuron under study, the other on the typical characteristics of natural images. Specifically, since V1 neurons are selective for stimulus orientation, most previous studies have resorted to simple oriented stimuli such as bars or gratings. These experiments usually begin with identification of the stimulus orientation to which the neuron responds most strongly in the classical receptive field, followed by the simultaneous presentation of iso- or cross-oriented stimulus content in the surround.<sup>3,4,7</sup> Other studies have instead presented natural images and varied stimulus size, such that there are “center only” and “center plus surround” conditions.<sup>8</sup> Common to both classic approaches is that the total number of unique stimuli per experiment represents a very, very small part of image space (Figure 1A).

What are the rules that govern whether surround stimuli suppress or enhance a neuron’s response to center stimuli? Previous work has shown that stimulus contrast,<sup>4</sup> receptive field structure,<sup>5,8</sup> and natural image statistics<sup>5,8</sup> all play a role. But how these factors interact with

each other has not been fully resolved. The issue at stake may be too complex to fully address in an experiment with a small set of preselected stimuli. Specifically, because the receptive field structure plays a critical role, the same stimulus configuration might yield opposite effects for different neurons.<sup>8</sup> This implies that it is only possible to formulate a specific hypothesis for a given neuron after some diagnostic measurements about receptive field structure have been obtained. Whatever *post hoc* hypothesis one might arrive at, due to the vast size of image space, it is extremely unlikely that the stimuli that are best suited to test this hypothesis are included in the experiment.

In this issue of *Neuron*, Fu et al.<sup>1</sup> leverage a recently developed closed-loop paradigm<sup>9,10</sup> to study contextual modulation in V1 neurons. Key to their approach is that the set of experimental stimuli is not determined in advance. Instead, the experiments navigate image space guided by specific hypotheses about the stimulus-response relation of the neurons under study. These experiments are technically challenging. They involve large-scale recordings, image-computable neural response models, *in silico* stimulus optimization, and *in vivo* validation (Figure 1B). In the first phase of the experiment, sparse noise stimuli and thousands of natural images of varying sizes were presented while neuronal responses in mouse V1 were recorded using two-photon imaging. These measurements were then used to train convolutional neural network models to predict V1 responses as a function of visual input. The critical innovation of this study is that these models were subsequently interrogated to identify cell-specific surround images that ought to maximally facilitate





**Figure 1. Image space opens up for visual neuroscience**

(A) The number of images shown per unit for several classic studies of center-surround interactions in V1,<sup>1,4–8</sup> plotted as a function of publication year. (B) The closed-loop experimental paradigm leveraged by Fu et al.<sup>1</sup>

or suppress the neuron’s response to an optimal center stimulus presented in isolation. To verify these predictions, in the third phase of the experiment, Fu et al. presented these synthesized stimuli to the same mouse and recorded from the same set of neurons, thereby closing the loop. Their measurements closely matched the predictions.

The approach developed by Fu et al. is intrinsically elegant and powerful. It allowed the authors to conduct large *in silico* experiments in “digital twins” of the neurons under study and to concentrate a substantial fraction of their experimental measurements in the parts of image space that are critical for the computational operations at play. As a result, the insights derived from this endeavor are rich and nuanced. The findings validate a major lesson learned from previous studies of macaque V1: contextual modulation is fundamentally shaped by the statistical regularities of natural scenes.<sup>8</sup> However, this work deepens our understanding by clarifying the complex interplay between stimulus contrast, receptive field structure, and natural image statistics. As it turns out, the key driver of the sign and strength of contextual modulation is not so much whether the image content in the surround is iso- or cross-oriented compared with the center. Instead, what matters is whether the surround completes the center pattern in a manner that is typical or atypical of natural images. The former case yields response enhancement, the latter case response suppression. Careful analysis of *in silico* models of macaque V1 validated this hypothesis.<sup>1</sup> It is an intriguing

idea that raises fundamental questions about the role V1 plays in creating perceptual experience. Should we understand these neurons as relaying simple sensory measurements to downstream circuits that in turn use these measurements to create perceptual interpretations? Or is the message contained in V1 activity a complex mixture of measurement and interpretation that is sculpted by both upstream and downstream computations? Fu et al. argue that the second view naturally aligns with their findings.

In sum, Fu et al. achieve an important advance in the study of contextual modulation in V1 neurons. Whereas stimulus selection in previous studies was guided by intuition, they develop a principled closed-loop approach. In doing so, they remove the enormous complexity of image space as a fundamental obstacle. The resulting insights into the computational principles that govern center-surround interactions in mouse and macaque V1 add depth and nuance to our understanding. Whether these principles generalize to other visual areas, sensory modalities, and animal species remains to be explored. The approach developed by Fu et al. provides a proven road map for this important endeavor.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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