A-MuLV-transformed pre-B cells resulted from the activation of Jak1 and Jak3 in the absence of cytokines. Jak1 and Jak3 were activated in Clone K cells treated with IL-7, whereas in A-MuLV-transformed pre-B cell lines, these kinases were constitutively active (Fig. 3) (11). In pre-B cells transformed with a temperature-sensitive mutant of v-abl, Jak1 and Jak3 were active at permissive temperatures, and upon a shift to nonpermissive temperatures, they became inactive (Fig. 3). Thus, in A-MuLV-transformed pre-B cells, the activities of Jak1 and Jak3 correlate with that of the v-Abl protein tyrosine kinase.

We next investigated the possible interaction between v-Abl and Jak1 or Jak3. Jak1 or Jak3 was immunoprecipitated from extracts of pre-B cells expressing the temperature-sensitive mutant of v-Abl. The v-Abl protein was detected in Jak1 and Jak3 immune complexes (Fig. 4) (21). Jak1 was also detected in v-Abl immunoprecipitates (Fig. 4B). These observations were confirmed with several other antibodies to Jak1 and Jak3 (11). We were unable to coimmunoprecipitate either Jak1 or Jak3 with the 150-kD c-Abl protein in the non-A-MuLV-transformed pre-B cell line Clone K (Fig. 4).

Two models have been proposed for the mechanism of growth factor independence in cells transformed by oncogenic forms of Abl (5, 7, 22, 23). According to one model, v-abl may increase the synthesis of RNAs encoding cytokines. Secreted cytokines could then bind their receptors and transduce their signals. Alternatively, v-Abl may abrogate the need for cytokines to bind to their receptors by interacting with components of cytokine signal transduction pathways. In an attempt to distinguish between the two models, we assessed the amount of RNA encoding IL-4 and IL-7 in the pre-B cells transformed with the temperature-sensitive mutant of v-abl. We were unable to detect IL-4 or IL-7 mRNAs by reverse transcription–polymerase chain reaction (RT-PCR) in these cells (11). In addition, supernatants from cultures of A-MuLV-transformed pre-B cell lines did not induce GAS binding activities in Clone K cells (11). Although, we cannot exclude the possibility that these transformed cells produce other cytokines, the lack of mRNA for IL-4 and IL-7 and our observation that Jak1 and Jak3 coimmunoprecipitate with v-Abl are consistent with the latter model. Our results suggest that A-MuLV constitutively activates the IL-4 and IL-7 signaling pathways. Constitutive activation of Jak-STAT signaling has also been observed in T cells transformed with human T cell leukemia virus–I (24). Activation of cytokine signal-transduction pathways might be a mechanism by which some transforming viruses induce proliferation of their target cells.

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Lateral Interactions in Primary Visual Cortex: A Model Bridging Physiology and Psychophysics

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Recent physiological studies show that the spatial context of visual stimuli enhances the response of cells in primary visual cortex to weak stimuli and suppresses the response to strong stimuli. A model of orientation-tuned neurons was constructed to explore the role of lateral cortical connections in this dual effect. The differential effect of excitatory and inhibitory current and noise conveyed by the lateral connections explains the physiological results as well as the psychophysics of pop-out and contour completion. Exploiting the model’s property of stochastic resonance, the visual context changes the model’s intrinsic input variability to enhance the detection of weak signals.

A characteristic feature of primary visual cortex (V1) in primates is its topographic organization into columns (I) of neurons responding to oriented stimuli within restricted regions of the visual field. A neuron’s classical receptive field (CRF) is defined as that region of visual space in which an individual stimulus will elicit a response. Neuroanatomical studies (2), however, have revealed an extensive network of long-range horizontal processes that extend far beyond the representation of the classical receptive field in cortex. While these lateral connections primarily link regions of cortex whose neurons prefer stimuli with similar orientations, the contribution of these connections in the processing of visual information remains unclear. Gilbert
(3), for instance, has suggested that the plexus of horizontal connections provides neurons with information about the visual context of a stimulus.

The meaning of visual context can be illustrated with two examples drawn from common experience. Suppose the visual scene consists of a large wheat field. Individual stalks of wheat pale in importance compared to the wheat field as a whole. Only a feature in the scene that is “different” should stand out—for example, a horizontal bench among vertical stalks—which corresponds to the psychophysical effect of “pop-out.” The effect of the visual context in this case is to decrease the redundancy of many nearly identical stimuli. In contrast, if the visual scene consists of a faded or smudged photograph, the visual system needs to use neighboring visual landmarks to complete incomplete features, such as broken or interrupted lines in the photograph. The effect of visual context here is the enhancement of weak stimuli, rather than the suppression of strong stimuli. Both pop-out and enhancement of weak signals have been studied in the psychophysical literature (4, 5).

We now suggest that both context effects have a neurophysiological correlate at the earliest stage of cortical visual processing, namely in V1. Recalling that the CRF represents a restricted region of visual space, we will denote any visual stimulus within the CRF of a V1 neuron as a center stimulus. Stimuli in the nonclassical receptive field (outside the CRF) will be referred to as surround stimuli.

Modulatory influences of surround stimuli on the response of a cell have been observed in physiological experiments in cats and primates. For high-contrast, well-tuned stimuli inside the CRF, the addition of similar stimuli outside the CRF leads to a suppression of the response (6, 7). On the other hand, when weak (subthreshold) stimuli are present inside the CRF, the addition of multiple similar stimuli in the surround produces a weak increase in the response (6–8).

We propose a model that explains the reversal of the context effect by allowing the net effect of the long-range lateral connections to be stimulus dependent. Specifically, the effect of lateral connections on a center cell is excitatory when the cell receives weak direct input from the lateral geniculate nucleus (LGN), and it is inhibitory when it receives strong input. This effect is a natural consequence of the impact of noisy input on the cell’s response and the differential characteristics of excitatory (pyramidal) cells and inhibitory neurons.

The model is a single-layer network of 10,000 excitatory and 10,000 inhibitory cells. Both excitatory and inhibitory cells respond to stimuli of a preferred orientation with individual action potentials. The network map of orientation preferences used was measured by optical imaging in macaque monkey (9) and scaled to the size of the model network. Within each orientation hypercolumn (defined as an aggregate of columns spanning all orientation preferences), excitatory cortico-cortical connections dominate for very nearby cells (10), whereas inhibitory connections are more widely spread (11). Long-range excitatory connections are made onto excitatory and inhibitory cells with similar orientation preferences (Fig. 1) (12).

The LGN input is organized in analogy to stimuli used in physiological studies of nonclassical receptive fields. We idealize the center stimulus as input to cells in one particular orientation column. Stimulation of the nonclassical receptive field (the surround) is simulated by providing input to surrounding hypercolumns. The surround stimulus is oriented either parallel or orthogonal to the center stimulus. The LGN input frequency is taken to be linearly related to stimulus contrast. To test how the modulation by the surround depends on the contrast of the stimulus, we vary the contrast (input rate) of the center stimulus while keeping the contrast of the surround stimulus constant. Figure 2A displays the effect of surround stimulus on the response rate of a typical neuron whose preferred orientation matches the center stimulus.

For high center stimulus contrast, the cell’s response is suppressed by about a factor of 2 for orthogonal surround and by nearly a factor of 3 for parallel surround (6). The stronger suppression of cells tuned to the same orientation is a physiological correlate of pop-out: Given the same surround stimulus, the cells that code for the singular (orthogonal) center stimulus respond more strongly.

For low center stimulus contrast, adding a surround stimulus of the same orientation increases the firing rate of the center cells. As shown in Fig. 2B, this increase lowers the perceptual threshold of detecting a stimulus when surrounded by parallel elements (13). The time course of the response is shown in Fig. 2, C and D, comparing a model neuron to the averaged temporal response of real neurons.

Our model accounts for the differing effect of the visual context on the response to weak and strong stimuli using physiologically plausible mechanisms. To analyze the mechanisms responsible for line completion and pop-out, we will consider separately the effect of mean net current and the effect of current fluctuations contributed by the surround.

The net current from the surround contribution depends on the level of activation of the cells responding to the center stimulus (14). Because the spontaneous background input to inhibitory cells in the model is lower than to excitatory cells, inhibitory cells will only be activated at higher external input rates. At low stimulus contrasts, the input from long-range lateral connections will only weakly increase the firing rates of inhibitory neurons; only long-range excitation remains, resulting in the line completion effect. Because the firing rate of inhibitory neurons increases faster than that of excitatory neurons as a function of input, the surround contribution becomes functionally inhibitory as the strength of LGN stimulation increases. The difference between nonorientation- and orientation-specific inhibition is responsible for the pop-out effect.
Hirsch and Gilbert (15) have shown that the analogous experiment of varying the strength of horizontal inputs produces similar results: Threshold microstimulation of the plexus of horizontal fibers results in excitatory postsynaptic potentials (EPSPs), whereas higher stimulus currents evoke di-synaptic inhibition that can counter and even overwhelm the laterally evoked EPSP.

As opposed to the common belief that noise is detrimental to information processing, the addition of noise by the surround actually improves the neural sensitivity (at low inputs) by increasing the slope of the response firing rate as a function of the contrast. Using noise to extend the dynamic range of a system is known in physics as stochastic resonance (16, 17).

Even when the net mean current contributed by the lateral connections is always inhibitory (independent of the center stimulus contrast), the fluctuations contributed by the surround can produce an increase in the firing rate for low center contrast (18). The differential excitatory and inhibitory cell responses and the response to stochastic input are thus jointly responsible for the context effect.

The context effect mediated by lateral connections described here can serve as a powerful computational mechanism for both line completion and pop-out. In the context of psychophysics, our model predicts that pop-out decreases for weak stimuli. Another model prediction is that the perceived stimulus intensity in the presence of surround stimuli is enhanced for low stimulus contrast and suppressed for high stimulus contrast; this was confirmed psychophysically (19). Physiological verification of these predictions requires that stimulus contrast be included as an independent variable in non-classical receptive field studies (20).

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14. We chose the same number of inhibitory cells as excitatory cells for reasons of computational efficacy. Each cell’s subthreshold membrane potential $V$ obeys the equation $C dV/dt = -g_{Na} (V - V_{Na}) + g_{L} (V - V_{L}) + g_{K} (V - V_{K})$, where $C$ is the membrane capacitance, $g_{Na}$ is the cell’s input resistance, and $g_{Na}$ and $g_{K}$ are excitatory and inhibitory synapti- c conductances, respectively. $g_{Na}$ is a calcium-dependent potassium conductance, and $V_{Na}, V_{L}, V_{K}$ and $V_{T}$ are the reversal potentials for sodium, chloride, and po- tassium, respectively. Spiking is modeled by an integrate-and-fire mechanism in which units that reach a threshold voltage are reset by subtracting the difference between the threshold voltage and the resting potential. The conductances change exponentially and depend on the number of synaptic events impinging on the cell. For unit $i$, the conductance is $\tau_i (dI/dt)_{i} = -g_{i} + \sum_{j} C_{ij} (V - V_{offline})$, where $\tau_i$ is the membrane input resistance, $\tau_i$ is the synaptic conductance, and $V_{offline}$ is a shorthand notation for whether the unit $i$ is excited in the previous millisecond, and $\sum_{j}$ is the summation over all of the units which is weighted by $C_{ij}$. Local, nonorientation-specific connections serve to implement the massive excitatory feedback of the classical microcircuit (10). Inhibitory cells are modeled as receiving fewer connections from LGN and from cortical areas other than pyramidal cells. Without stimulus input, they are further away from firing threshold than the excitatory cells, as indicated by their lower spontaneous firing rate. For each cell type, the external input $x_i$ follows a Poisson distribution and has two components. The first is the stimulus-specific LGN input: $g_i (V - V_{offline})$, where $g_i$ is the cell’s preferred orientation. Spontaneous firing results from the second component of $g_i$ that groups together all inputs from outside V1 and LGN. Excita- tory cells are subject to firing rate adaptation as given by a simple model of the calcium-dependent potas- sium conductance: $\tau_c (dI/dt)_{c} = -g_{c} + K \psi_{c} - V_{offrebound}$, where $K$ is a positive constant. Spikes arriving from inhibitory cells open conductances with both additive and multiplicative (shunting) effects.

The time course of inhibitory conductances is an- alogous to that for excitatory conductances: $\tau_e (dI/dt)_{e} = -g_{e} + c \psi_{e} \psi_{offrebound} + w/\tau$. By assum- ing that inhibition occurs also on the apical shunt of the dendrite, we can model the shunting of excitatory current phenomenologically (following L. F. Abbott, Physiol. Rev. 1988, 534 (19932) by multiplying $\tau_{off}$ by a factor of $1 - \psi_{o}$. By assuming that inhibition occurs also on the apical shunt of the dendrite, we can model the shunting of excitatory current phenomenologically (following L. F. Abbott, Physiol. Rev. 1988, 534 (19932) by multiplying $\tau_{off}$ by a factor of $1 - \psi_{o}$.

13. In analogy to the psychometric curve in two-alterna- tive-forced-choice experiments (5), we measured in the model the ‘‘pure’’ curve (Fig. 2A) on the basis of spike counts of single cell within the classical receptive field (CRF) to verify that the increase in firing results in a lower detection threshold for the central target.
An Internal Model for Sensorimotor Integration
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On the basis of computational studies it has been proposed that the central nervous system internally simulates the dynamic behavior of the motor system in planning, control, and learning; the existence and use of such an internal model is still under debate. A sensorimotor integration task was investigated in which participants estimated the location of one of their hands at the end of movements made in the dark and under externally imposed forces. The temporal propagation of errors in this task was analyzed within the theoretical framework of optimal state estimation. These results provide direct support for the existence of an internal model.

The notion of an internal model, a system that mimics the behavior of a natural process, has emerged as an important theoretical concept in motor control (1). There are two varieties of the internal model: (i) forward models, which mimic the causal flow of a process by predicting its next state (for example, position and velocity) given the current state and the motor command; and (ii) inverse models, which invert the causal flow by estimating the motor command that caused a particular state transition. Forward models have been shown to be of potential use for solving four fundamental problems in computational motor control. First, the delays in most sensorimotor loops are large, making feedback control too slow for rapid movements. With the use of a forward model for internal feedback, the outcome of an action can be estimated and used before sensory feedback is available (2, 3). Second, a forward model is a key ingredient in a system that uses motor output (also called efference copy) to anticipate and cancel the sensory effects of movement (also called reafference) (4). Third, a forward model can be used to transform errors between the desired and actual sensory outcome of a movement into the corresponding errors in the motor command, thereby providing appropriate signals for motor learning (5). Similarly, by predicting the sensory outcome of the action without actually performing it, a forward model can be used in mental practice to learn to select between possible actions (6). Finally, a forward model can be used for state estimation in which the model's prediction of the next state is combined with a reafferent sensory correction (7). Although shown to be of theoretical use, the existence of an internal forward model in the central nervous system (CNS) is still a topic of debate.

When we move an arm in the absence of visual feedback, there are three basic methods the CNS can use to obtain an estimate of the current state—the position and velocity—of the hand. The system can make use of sensory inflow (the information available from proprioception), it can make use of integrated motor outflow (the motor commands sent to the arm), or it can combine these two sources of information by use of a forward model. To test between these possibilities, we carried out an experiment in which participants, after initially viewing one of their arms in the light, made arm movements in the dark. Three experimental conditions were studied, involving the use of null, assistive, and resistive force fields. We assessed the participants' internal estimate of hand location by asking them to localize visually the position of their hand at the end of the movement (8). The bias of this location estimate, plotted as a function of movement duration, shows a consistent overestimation of the distance moved (Fig. 1). This bias shows two distinct phases as a function of movement duration: an initial increase reaching a peak of 0.9 cm after 1 s followed by a sharp transition to a region of gradual decline. The variance of the estimate also shows an initial increase during the first second of movement after which it plateaus at about 2 cm². External forces had distinct effects on the bias and variance propagation. Whereas the bias was increased by the assistive force and decreased by the resistive force, the variance was unaffected.

These experimental results can be fully accounted for if we assume that the motor control system integrates the efferent outflow and the reafferent sensory inflow. To establish this conclusion, we developed an explicit model of the sensorimotor integration process, which contains as special cases all three of the methods referred to above (9). This model is based on the observer framework (7) from engineering in which the state estimator (or observer) has access to both the inputs and outputs of the system. Specifically, the input to the arm is the