Inhibitor of DNA in Lymphocytic Cells

The report presented by Houck et al. (1) deals with a specific inhibitor of the lymphoid tissue. Their results are almost identical to the ones that I have published (2). Our data were the following: the inhibitor was a protein with a molecular weight of 45,000; it inhibited DNA synthesis in vitro in human lymphocytic cell lines, but did not inhibit RNA or protein syntheses. When our tissue extract was injected into adult (DBA/2 x C57Bl6) F1 mice it was able to (i) inhibit cell proliferation in the lymphoid tissue, (ii) decrease the number of immune competent antibody forming cells in the spleens of mice immunized by sheep red blood cells, and (iii) inhibit the growth versus host reaction when given to the donors. In vitro it blocked the blastic transformation induced by phytohemagglutinin (PHA(P)), by a specific antigen or by allogenic cells in mixed leukocyte culture (MLC), as measured by tritiated thymidine incorporation into material precipitable by acid. When we injected our protein extract (8 mg/d) into mice for 4 days, the lymphocytes of the treated animals showed a 40 percent decrease in their transformation rate induced by PHA or by allogenic cells in MLC.

The principal difference between our extract and the one obtained by Houck et al. (1) is that ours was obtained from bovine spleen and theirs from rat lymph node and spleen.

However, despite the similarity between our results and the ones which appeared in the report by Houck et al., our work is not cited.

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Does the Striate Cortex Begin Reconstruction of the Visual World?

Pollen et al. (1) have proposed that the output of each complex cell in the visual cortex of a cat represents a Fourier component of the light intensity distribution on the retina. This hypothesis implies several properties of complex cells which are inconsistent with published evidence. If the firing pattern of a neuron in the visual system provides information about phase and amplitude for a spatial frequency, then:
(i) Its output should be independent of position of an image in the receptive field except for a frequency-dependent phase angle. Pollen et al. indicate that this requirement is satisfied in that complex cell responses are invariant within their receptive fields except for the peak response latency. Yet examination of the published responses of complex cells reveals significant variation beyond that in peak response latency. This variation is evident in both individual spike trains (2) and average response histograms (3).
(ii) The output of a neuron that represents a Fourier component should be a linear function of the effective stimulus magnitude. The output of a complex cell cannot be a linear function of the logarithm of image intensity for all images if, as argued by Hubel and Wiesel (2), simple cells provide the principal inputs to complex cells. For example, if a stimulus falls in an inhibitory portion of the receptive field of a simple cell, it decreases the firing rate of that cell. Sufficient inhibition can silence the simple cell, so that it gives no output when stimulated in a neighboring excitatory region until the excitation exceeds inhibition (4). Thus the response of a simple cell may be a nonsmooth function of intensity, and the response of complex cells postsynaptic to it must therefore be nonlinear. Any cell having a receptive field with excitatory and inhibitory portions must have a nonlinear intensity-response curve for some images. Hence, by the same argument, if any such cells are afferent to complex cells, the intensity-response curve for a complex cell must be nonsmooth and must depend on the location of the image in its receptive field.

The Fourier model is deficient in two other respects.
1) In the simplest neuronal Fourier analyzer the amplitude and phase of response to a constant image would be independent of time at each frequency.
2) If the image varied in time, a linear, time-independent transform could be used to predict the output of the analyzer. If, however, an array of neurons gives a time-varying response to a constant input, the transform required to convert input to output must be time-dependent. In such a case any hypothesis that the array is a Fourier analyzer must specify this transform. Without the transform it is impossible to test the hypothesis by predicting the response of the array to novel stimuli.

The instantaneous response of a complex cell depends on the recent history of intensity distributions on the retina in at least two ways. Its response to a distribution fixed on the retina varies with time after the stimulus goes on or off, as the complex cell and cells different to it adapt (2). If the distribution moves across the retina, the firing rate depends on the direction and speed of motion of the image (3). Hence if complex cells present a Fourier transform, the amplitudes and phases must be history-dependent. The proposal by Pollen et al. does not specify the nature of the time-dependent transform which these data require. Furthermore, if lateral geniculate or simple cells different to complex cells adapt in response to a constant stimulus, information about the stimulus is lost, and the "conservation of information" which Pollen et al. posit for processing through these stages does not obtain.

2) Pollen et al. cite a study by Campbell et al. (5) on cat visual cortical cell responses as showing that at least one such cell has " . . . the sharp cutoff on each side of the preferred spatial frequency that would be expected according to a model based on Fourier theory." However, most visual cortical cells in this study were no more selective of a preferred frequency than lateral geniculate cells on the low frequency side of the frequency that gives peak response, and none was more selective of higher frequencies. Moreover, retinal ganglion cells are much more frequency-selective than those at either higher level (6). In fact, Campbell et al. (5, p. 232) paid little attention to the cortical responses at lower than optimal frequencies because " . . . the variations in the form of the low
frequency end of the curves prevented any meaningful analysis of this portion of the curve."

Pollen et al. also cite a series of psychophysical experiments by Campbell and his associates (7) as added weight for their conclusions because these studies "... are in the main so consistent with their predictions according to Fourier theory." In fact, the psychophysical experiments often showed great disparity from their predictions in the range of lower frequencies—the same range in which the "spatially selective" cortical cells differ from other cortical cells. Campbell et al. recognized this fact and were careful not to make unwarranted conclusions about where the psychophysically demonstrable processing of images into Fourier components might occur.

Violation of any of the criteria that follow from the definition of a Fourier transform indicates that a complex cell does not code phase and amplitude for a Fourier representation. Although the brain may at some level use frequency analysis in processing visual information, we conclude that complex cells do not present a Fourier transform of retinal images.

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Pollen et al. (1), in order to explain how we see an object as the same object regardless of changes in its position and apparent size, offer the hypothesis that the striate cortex performs a "Fourier transform." Invariance of pattern recognition with respect to translations and expansions of the monocular retinal image is not the only form of visual stimulus equivalence, nor even the most striking one. As we watch a dog romp on a lawn, it rotates in three dimensions, changes shape, passes from light into shadow across boundaries, and presents itself against a varying background. It is seen as one and the same dog, although a "Fourier transform" of the retinal image would be undergoing changes not only in amplitude and phase, but in form. Whatever mechanism may account for stimulus equivalence in the face of changes of shape, background, and incident light should easily be able to handle invariance with respect to translation and expansion— In the present state of our ignorance, there is no need to postulate a separate mechanism to handle translations and expansions.

The hypothesis that the striate cortex performs strip integrations and a "Fourier transform" is not a parsimonious explanation of stimulus equivalence; but lack of parsimony does not prove it to be false. It is clear that the cortex performs some transformation of the information arriving from the geniculate, and it has indeed been shown that some cortical cells respond most vigorously to a narrow range of spatial frequencies. However, Fourier components share this property with an infinity of other transformations. While it is true that the Fourier components are the only linear functionals on the real line or the circle whose absolute values are translationally invariant, it is clear that the firing rate of a complex cell is neither a linear nor a translationally invariant transform of the logarithmic intensity distribution on the retina. A frequency cannot be negative. Therefore, as Pollen et al. show in their figure 1A (1), the frequency versus intensity curve for a cortical cell has a kink at the threshold intensity—it is not linear. Translational invariance is incompatible with boundaries. It is not allowed to break down at the edges of a receptive field. Moreover, contrary to the assertion of Pollen et al. (1), translational invariance is incompatible with the experimental evidence, even for stimuli confined within the boundaries of the receptive field of a feline complex cell, as is shown in detail by Pettigrew et al. (2).

Since the "Fourier transform" which Pollen et al. imagine the complex cells to calculate cannot be a Fourier transform in the mathematical sense (3), nor even a close numerical approximation to it, it is not clear just what they imagine the transform to be. It cannot be a simple spatial average of strip integrals, for such an average would not show the pronounced sensitivity to direction of movement which is a striking feature of complex cells in the cat (2).

Not all the input to the striate cortex comes from the lateral geniculate body. Even in anesthetized animals, it has been shown that vestibular input, for example, can alter the orientation of trigger features for feline simple cells (4). On introspective grounds, we might doubt that anesthetized cats perform visual pattern recognition at all. In awake cats, the cortex must be played upon by many extrageniculate inputs and feedbacks which may well be crucial to stimulus equivalence and discrimination.

Pollen et al. propose that objects may be located in visual space by a phase angle code in the striate cortex. In fact, there is reason to believe that the location of objects in visual space does not require the geniculo-striate system at all, but is associated with the superior colliculus (5).

In sum, the theory proposed by Pollen et al. (1) is not a parsimonious explanation of visual stimulus equivalence, it is not compatible with the mathematical properties of the Fourier transform, it is contradicted by experimental evidence, and it imputes to the striate cortex functions which appear to be performed by other structures.

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Mittenthal et al. (1) and Kripke (2) have questioned our model of the processing of visual information (3) on various grounds, none of which we believe offer any serious problem. Both papers correctly point out that certain complex cells in the study of Pettigrew et al. (4) show considerable variations in response amplitude as a function of the position of moving slits. We studied those complex cells that responded well to stationary spots or slit stimuli. It was already known that about one-fifth
of this population have nonuniform receptive field response properties (5). Complex cells also exist which respond readily to moving stimuli but only weakly to stationary stimuli; but it seems unlikely that these cells are prominently involved in the processing of visual scenes fixed upon the retina. There are also complex cells that fire selectively to light and dark borders rather than to slits. Thus, on the basis of stimulus specificity, receptive field uniformity, and response to movement, there must be at least four complex cell populations. Nevertheless, in the static situation the majority of responding complex cells have uniform receptive field properties (5), and our own work, both the published report [figure 1C in (3)] and that in preparation, confirms this finding.

Various technical factors make this experiment rather difficult. It may be very difficult to determine the optimal orientation of a slit to better than 5 or 10 deg and to locate precisely the edges of the receptive field. Slight displacements either in rotation or translation can lead to weaker responses at receptive field borders because the slit may be only partly within the receptive field of the cell under study. Such factors might explain the weaker responses at the receptive field borders in figure 4, A and D, of the paper by Hubel and Wiesel (5). Even well within receptive field borders, variations may be seen from one stimulus to the next, even for the same slit placement. An example of this sort of variation is shown in figure 4, B and C, of the same paper. The second response in figure 4B is stronger than the first and perhaps not that different from the second response in figure 4C. However, there is no way for us to know whether the response differences are due to adaptive effects of previous stimulation, technical or statistical factors, or whether the differences reflect some real anisotropy in the receptive field which may or may not be significant within the overall processing of visual information.

Mittenthal et al. (1) are also concerned with the analysis of images varying in time. We chose to consider the simplest case—the analysis of a static pattern. We noted that even stationary images are "sampled" during discrete intervals, some as brief as 20 msec. To some extent the processing of time-varying images depends upon processing in sequential visual frames. To what extent perception is modified by changes in the image during these frames seems to us not fully known and in any case a problem beyond the scope of present work.

It is true that complex cells tend to adapt to stationary light stimuli fixed upon the retina. In normal vision (unlike the experimental situation in which the eye muscles must be paralyzed) rapid ocular tremors and frequent microsaccadic eye movements help to minimize retinal adaptation. Central adaptation can occur, especially when subjects fixate for long periods on spatially redundant material (6). However, as long as the time periods for adaptive effects are longer than the brief periods required for the analysis of visual frames, they offer no difficulty for the accurate analysis of a given frame. It is true that adaptation effects, especially selective effects, modify perception of certain images (6). In such cases the adaptation "information" is used by the nervous system and must be known by the experimenter if he is to make correct predictions about the perception of a new visual image.

Our appeal to a "conservation of information" principle was intended to show how the available visual information might be handled through a set of sequential transformations in the visual cortex. Adaptive effects are not relevant here; information about a visual scene may be lost when we adapt to the scene, but this is true regardless of how the neural network processes the remaining superthreshold data. We believe that one of the most attractive features of our model is that the transformations we have proposed express an equivalent content of information at three successive stages (point-to-point mapping, followed by strip integration, and decomposition into spatial frequency channels) and that each of the three stages is readily identified with a known class of cells.

Mittenthal et al. correctly note that if an image moves across the retina, the firing rate of some complex cells depends on the direction and speed of the image. We do not believe that the transform operating on stationary images should be corrected to allow equal discrimination of patterns moving across a fixed retina. Visual acuity of an object (for example, this page) is impaired if the object is swept across a fixed retina; however, this is not the normal situation when the best resolution of fine detail in moving objects is required. Rather, the brain keeps the object to be examined as stationary as possible upon the fovea, by a combination of compensatory head and eye movements (7, 8).

It is stated by Mittenthal et al. that the output of a complex cell "...cannot be a linear function of the logarithm of image intensity for all images." Certainly, as they say, if a strong stimulus falls within the inhibitory portion of the receptive field of a given simple cell then the activity of the cell may be cut off entirely. Presumably, however, there are a number of overlapping simple-cell receptive fields with both excitatory and inhibitory field centers, and we see no basis for an a priori conclusion about the nature of the network output, which is the relevant entity.

We might also point out that while rigorous Fourier analysis is a linear process, it is well known in communications theory that nonlinear operations which severely distort the amplitude relations of a signal may have a remarkably small effect on the signal spectrum—that is, on the amplitudes of its Fourier coefficients. A voice waveform may, for example, be logarithmically compressed, clipped, or even infinitely clipped (so that it assumes everywhere a value of +1 or —1) without destroying its intelligibility or fundamentally altering its spectrum. The same would apply to the spatial Fourier components of a visual scene and might help to explain why our pattern-recognition capabilities are not grossly affected by such common nonlinearities as overexposed photographs and poorly adjusted television pictures.

We share with Mittenthal et al. a concern for the not-very-sharp frequency selectivity of neurons in the striate cortex. However, it has been shown that gratings differing in spatial frequency by only 4 percent can be distinguished from each other (9), and we therefore might suspect that more sharply tuned neurons will be found in higher levels of the visual system, although this need not be the case (10). Earlier questions concerning responses to very low spatial frequencies have been largely resolved by recent psychophysical experiments by Campbell et al. (11).

Kripke (2) is mistaken if he believes that the visual system generalizes as well for changes in pattern orientation (6) and three-dimensional rotation (12) as it does for changes in size and translation. This point was demonstrated very clearly by Shepard and Metzler (12) on the cover of a recent issue of Science. The comment about negative frequencies and a "kink" in the response versus
intensity curve at threshold is completely irrelevant. Any model of the processing of visual information in the brain need not be concerned with the brightness distribution existing in the outside world, but only with the perceivable part of it that exceeds biological thresholds.

Kripke (2) states that translational invariance is incompatible with boundaries. Although each cell in the striate cortex deals with only a restricted region of visual space, groups of cells deal with overlapping receptive fields that together cover all of visual space. We have suggested (3) that a Fourier transform begins in the striate cortex and have noted that the "... complete description of any object is not achieved until some form of 'read-out' of the information in all complex cells over the involved regional of visual space is established." In higher areas in the brain there are a number of cell types that respond to slits over a very wide region of visual space (13-15), and it is in these areas that one might look for completion of the transform. If the transform is completed, then there should exist a class of neurons that respond weakly to one slit of optimal width and orientation but much more strongly to an extended sine wave grating of the appropriate spatial frequency and orientation. These cells would not be bothered by the limited receptive field boundaries at previous stages.

The problem of vestibular inputs to the striate cortex raised by Kripke is a complicated one. Their function and significance must be carefully considered, as is done by Horn and Hill (16) and by Spinelli (17). Kripke also questions the relevance of studies on anesthetized animals for the problem of pattern recognition in awake animals. It has been shown in both awake cats (18) and monkeys (19) that receptive field properties are essentially independent of anesthesia, although the responses are weaker in the anesthetized animal.

Finally, Kripke has confused the localization of a visual stimulus, which depends upon the superior colliculus, with the problem of pattern recognition, which depends upon the striate cortex (20).

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Intracisternal A Particles and C Particles

The RNA tumor viruses have been grouped together because, as the term implies, they are RNA viruses which induce neoplasia. They consist of the avian leukosis-sarcoma complex, the mammary tumor virus (MTV), and the murine and feline leukemia-sarcoma complexes.

While differing in morphological and immunological detail, they as a group have certain essential characteristics.

As do the myxo- and paramyxoviruses, they replicate by budding from the plasma membrane or into vacuoles of infected cells.

With the exception of MTV all of the members of this group are type C viruses as defined by Bernhard (1). Extracellulat particles possess a centrally located nucleoid surrounded by a loosely fitting envelope. In the process of budding, type C viruses develop an envelope formed from the plasma membrane. They also develop an intermediate layer comparable to the capsid layer of DNA viruses, such as herpes, and naked RNA viruses, such as reovirus. Inside the intermediate layer is a heavily electron-dense layer forming the inner portion of the nucleocapsid. Thus the "immature" type C virion possesses three distinct components—the envelop, the intermediate layer, and the inner electron-dense shell. Depending on the species in which the virus is indigenous, the outer diameter of the virion may vary from 95 to 110 nm.

The intracisternal A particles of mice (2) bud only from the endoplasmic reticulum, and their total diameter averages 70 nm. They are not seen in an extracellular position in biopsy material. Thus the particles described in tissue culture cells derived from a rhodomyosarcoma by Stewart et al. (3) are not, strictly speaking, type C particles, since they are not seen extracellularly and do not bud from the plasma membrane. The "immature" particles do not appear to possess an intermediate layer, yet some particles (mature?) possess electron-dense centers. Thus while they correspond in certain respects to the intracisternal A particles of the mouse, they differ in this essential respect. Further morphological and other studies will be needed before these particles can be placed in any particular category.

On the other hand, the particles found budding from the plasma membrane and present extracellularly in the tissue cultures isolated from a pulmonary adenocarcinoma (3) possess all of the characteristics of type C virions.

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