this is a general mechanism in the many fishes that presumably have the *Schreckstoff* system — let alone in zebrafish about whose ecology deplorably little is known — remains an open question.

The chemical nature of the *Schreckstoff* component identified by Mathuru and colleagues [3] and its being a constituent of mucus do suggest that the alarming function could be a secondary by-product. But then, what about the club cells? Surprisingly, there is evidence that their alarm function might also only be secondary. When fathead minnows are exposed to parasites, pathogens or UV light, they increase the number of club cells in the skin, an effect that is inhibited by immuno-suppresion [20]. So, after all, the *Schreckstoff* could just be a by-product of other protective functions that enhance fitness of the bearer — much like its serendipitous discovery was the by-product of a summer holiday and the study of hearing in fish. And much like that first minnow that von Frisch cut, the presumed evolutionary enigma of *Schreckstoff* might just disappear. Oh, by the way, did we mention what the new Schreckstoff component was? Oligosaccharides of chondroitin-4-sulfate and chondroitin-6-sulfate.

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Active Vision: Fixational Eye Movements Help Seeing Space in Time

The significance of the miniature eye movements that we make during visual fixation has been intensely debated for the last 80 years. Recent studies have revealed that these motions of the eyes fulfill an important functional role: helping to extract useful information from natural scenes.

Igor Kagan

We live in a dynamic environment, in which the visual scenery changes from one instant to another. Some of these changes are caused by external events, such as the movement of trees in the wind. But even when the world is stationary, our own movements constantly shift the projection of the visual scene on the retina. Even when we have no intention to look around, but try to maintain a steady gaze during fixation, our eyes are still in constant motion because of the instability caused by fixational eye movements: slow ocular drifts and fast abrupt shifts called fixational saccades or microsaccades. For decades, the role of these self-generated retinal motions has been an important and controversial issue, fraught with methodological complications [1]. Are these movements useful, irrelevant, or damaging to our vision? Despite progress in elucidating the perceptual and neuronal effects of fixational instabilities in specific, artificial laboratory settings, a much needed conceptual and computational framework for understanding the role of fixational eye movements in natural vision has been lacking. A series of recent advances by Rucci and colleagues, including the most recent study by Kuang *et al.* in this issue of *Current Biology* [2], make a crucial step towards this fundamental understanding, demonstrating that fixational eye movements are an integral part of early visual processing strategy to efficiently analyse and encode natural scenes.

The idea that fixational eye movements may be useful for improving the perception of fine spatial details has been originally proposed by Hering. This notion has been developed further in dynamic theories of visual acuity, in the middle of the last century (see [3] for review), and recently has received renewed interest in the dynamic theory of vision put forward by Ahissar and Arieli [4]. Those theories suggested that fixational jitter contributes to our ability to resolve patterns smaller than one or few retinal photoreceptors. Until now, however, the empirical evidence for or against these theories has been inconclusive, in a large part because of the technical limitations of experiments that eliminated retinal motion — so-called 'image stabilization' studies. With the help of advanced stabilization techniques, Rucci and colleagues [5] have convincingly demonstrated that fixational eye movements indeed improve the discrimination of high spatial frequency stimuli — the fine spatial features of an image. This result contradicts a perhaps more intuitive notion that fixational instability could be detrimental for the tasks demanding high visual acuity (for example [6]). But how and at which stage of visual processing does the enhancement come about?

The new study by Kuang *et al.* [2] answers these questions by showing that the statistics of normal fixational eye movements match the statistics of natural images, such that their interaction generates spatiotemporal inputs optimized for processing by retinal ganglion cells. The authors recorded the eye movements of human subjects viewing static natural images with a high precision and analyzed the resultant 'natural movie' inputs to the retina using spectral analysis. In the absence of eye movements, the spectral power of static natural images declines steeply at high spatial frequencies (which represent fine details). This means that natural scenes are dominated by relatively uninformative low frequencies and extensive spatial correlations, making the visual inputs to the retina highly redundant. This is detrimental, as the transmission capacity from retinal photoreceptors to the brain, and the brain's computational resources, are limited. In the reconstructed retinal 'movies', however, the power was equalized over a wide range of spatial frequencies, with *attenuated* contribution of low spatial frequencies and *accentuated* contribution of high frequencies, which represent informative features such as edges. The equalization occurs because spatial and temporal characteristics of fixational eye movements happen to specifically counterbalance the spectral distribution of natural scenes.

Thus, fixational eye movements transform the spatial information of the external scene into temporal modulations in the input to the retina. This spatiotemporal *reformatting* is crucial for neural coding, as it matches the range of peak spatiotemporal sensitivity of retinal neurons in primates. Furthermore, it also provides an explanation for the lack of blurring during fixational instability. With normal eye movements, low spatial frequency power (the blurred image) is concentrated at zero temporal frequency, at which retinal ganglion cells are only weakly responsive. These effects are illustrated in the computational model of retinal and lateral geniculate nucleus neurons based on the data from macaque monkeys. Unlike static scenes, 'natural movies' elicited responses that decorrelated the activity across the population, retaining only a subset of active neurons with synchronized modulations emphasizing contours.

These findings radically challenge the current thinking about a central question in the visual sciences: how the tuning of neurons in the visual system is optimal for vision. Recent theories assume that following ecological constraints and evolutionary adaptation, properties of sensory systems reflect the statistical structure of signals to which they are exposed [7,8]. (Admittedly, the scenery underwent some changes in the course of primate evolution, especially in the last two millennia, but natural environments and man-made landscapes and interiors share similar spectral characteristics.) The prevalent view is that visual neurons filter input signals to achieve efficient extraction of informative features, for example edges, and to create neural representation with minimal redundancy [9]. But according to the new results [2], fixational eye movements eliminate input redundancies and emphasize important features before any neural processing takes place. Thus, the principles of efficient coding based on static natural images cannot explain the response characteristics of retinal neurons and have to be revisited with the effects of fixational instability taken into account.

One conspicuous aspect in the study of Kuang *et al.* [2] that needs to be highlighted is the scarcity and striking functional nonsignificance of microsaccades, as compared to the major effects due to slow fixational drifts. It is notable that much of the recent research on the fixational eye movements in humans and monkeys has been focusing exclusively on microsaccades, although few modeling studies also considered drifts [10,11]. Microsaccades are very noticeable events, easy to detect, quantify and analyze in laboratory settings, and they elicit strong but transient neuronal responses in the visual system by abruptly moving the retinal image [12–15]. However, the frequency of microsaccades in natural vision is low [1,16], and the importance of these events for visual processing in everyday life may have been exaggerated. In fact, the same principles of oculomotor control suggest that there is nothing special about microsaccades as compared to larger saccades [16,17]. On the other hand, the eyes move continuously between microsaccades or larger saccades, and most of our visual experience takes place in these ubiquitous drift periods. So far, the role and effects of fixational drifts have received little attention. The major contribution of drifts to the effects described in Kuang *et al*. [2], and strong activation during the drift periods in a subset of cortical neurons [14,18], call for rectification of this bias.

After a long hiatus following pioneering studies and heated but inconclusive debates in the 60s of the last century, the research on the role and consequences of fixational eye movements intensified dramatically in the last decade, owing to new methods available for human psychophysical studies and neurophysiological studies in awake behaving monkeys [19]. Several important findings (of which only some are discussed here) significantly advanced our understanding of fixational instabilities. However, some recent research

resulted in more controversy. For example, 'prevention of image fading' is the traditional hypothesis used to justify the existence of fixational eye movements. This hypothesis, which has not been well defined and used by different authors with different meanings, has remained very contentious [1,19,20]. Regardless of the doubtful necessity of preventing fading in natural viewing conditions, the study by Kuang *et al.* [2] convincingly shows that the function of fixational instability goes well beyond that. Fixational eye movements do not merely prevent fading and 'refresh' scenes and neural responses, they structure them in a very specific manner into optimized visual representations. The view that fixational eye movements, and in particular fixational drifts, are an integral component of visual perception represents an important conceptual advance for this turbulent field, and will certainly inspire further investigations. Promising future directions include the extension to more natural head-free experiments, combining the study of fixation periods with post-saccadic retinal and extraretinal effects, and testing model predictions in physiological recordings in retinal, thalamic, and cortical pathways.

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Subcellular Organization: Change of Phase in Partitioning the Cellular Milieu

Spatial organization and segregation are essential for the function of a complex and crowded cellular machine. New work demonstrates liquid–gel phase separation, both *in vitro* and *in vivo*, driven by the valency of constituent proteins.

Joe Swift and Dennis E. Discher*

The interior of a cell is densely packed with macromolecules that occupy 20–30% of the available volume — a fact often illustrated by the artwork of D.S. Goodsell [1]. Stresses that arise from crowding are less apparent in a test tube of dilute protein and cause changes in diffusion, stability, and reactivity [2]. The machinery in the cell must therefore be carefully managed and compartmentalized in order to ensure its function and specificity. While membranes often delimit organelles, exceptions include Cajal bodies [3] and P bodies [4]. Membrane-free bodies are compositionally distinct from the bulk and often enriched in proteins and nucleic acids capable of multiple simultaneous binding interactions, a property referred to as 'multivalency' [5,6]. The idea of a sharp phase separation that is triggered by a critical concentration of self-interacting macromolecules is familiar to polymer scientists [7], but the extent to which nature utilizes this phenomenon as a mechanism for cellular organization is poorly understood.

A recent publication in *Nature* by Li *et al.* [8] uses synthetic protein constructs to show that interactions between multivalent proteins can drive liquid–gel phase separation both in solution and when expressed in cells. Proteins were engineered to contain up to five repeats of either the Src homology 3 (SH3) domain or the proline-rich motif (PRM), a receptor–ligand pairing found in signaling pathways [9]. Mixing the two constructs *in vitro* caused spontaneous formation of spherical droplets of around 50 μm in diameter. Consistent with polymer theory, the propensity for phase separation was increased with concentration and valency. Protein was concentrated approximately 100-fold in the droplets relative to bulk, with both components present in equal quantities. Coincidently, this condensation of