This work demonstrates a remarkable convergence of experimental, theoretical, and computational approaches to studies of development. Indeed, live imaging of biochemical oscillations, optogenetic perturbations, particle image velocimetry, and computational fluid dynamics play equal roles in offering a thorough and satisfying explanation for a critical developmental transition. Some of these approaches have been enabled by studies of self-organized cytoplasmic flows in other systems, such as the early *C. elegans* embryo (Mayer et al., 2010). In the future, it will be interesting to determine whether the proposed mechanism for self-organized nuclear spreading is robust to spatial variations in placement of the first zygotic nucleus and to establish which substrates of PP1 are most critical for the emerging dynamics. Addressing these questions should provide valuable insights into the functional capabilities of self-organizing processes in early embryos.

REFERENCES

Deneke, V.E., Puliafito, A., Krueger, D., Narla, A.V., De Simone, A., Primo, L., Vergassola, M., De Renzis, S., and Di Talia, S. (2019). Self-Organized Nuclear Positioning Synchronizes the Cell Cycle in Drosophila Embryos. Cell *177*, S0092-8674(19)30269-7.

Foe, V.E., and Alberts, B.M. (1983). Studies of nuclear and cytoplasmic behaviour during the five mitotic cycles that precede gastrulation in Drosophila embryogenesis. J. Cell Sci. *61*, 31–70.

Mayer, M., Depken, M., Bois, J.S., Jülicher, F., and Grill, S.W. (2010). Anisotropies in cortical tension reveal the physical basis of polarizing cortical flows. Nature *467*, 617–621.

Peter, I.S., and Davidson, E. (2015). Genomic Control Process: Development and evolution (Academic Press).

Rabinowitz, M. (1941). Studies on the cytology and early embryology of the egg of Drosophila melanogaster. J. Morphol. *69*, 1–49.

Royou, A., Sullivan, W., and Karess, R. (2002). Cortical recruitment of nonmuscle myosin II in early syncytial Drosophila embryos: its role in nuclear axial expansion and its regulation by Cdc2 activity. J. Cell Biol. *158*, 127–137.

von Dassow, G., and Schubiger, G. (1994). How an actin network might cause fountain streaming and nuclear migration in the syncytial Drosophila embryo. J. Cell Biol. *127*, 1637–1653.

Insight into the Neuron's Insight

Arash Afraz[1,*]

[1]Unit on Neurons, Circuits and Behavior, Laboratory of Neuropsychology, National Institute of Mental Health, National Institute of Health, Bethesda, MD 20892, USA

*Correspondence: arash.afraz@nih.gov

https://doi.org/10.1016/j.cell.2019.04.019

In this issue, Ponce and colleagues use a generative closed-loop system to evolve synthetic images to explore the response properties of neurons in the inferior temporal cortex of non-human primates. The results reveal an unbiased assessment of feature selectivity in a high-level visual area involved in object recognition.

The Elephant in the Dark Room

Put your fingers on the sides of your head, slightly above and behind your ears. Under your fingertips, inside your skull, are neurons that fire vigorously every time you look at faces and various complex objects. It is commonly thought that we and our primate relatives use those neurons, located in the inferior temporal cortex (IT), for recognizing faces, animals, and objects. Yet, identifying the specific features of what these neurons respond to has been a challenge for systems neuroscience for the past three to four decades. For example, imagine you are recording from a random neuron in your IT, listening to its activity as you look at different images and exploring what that neuron likes most. You look at pictures of 10 different objects and the neuron responds to one of them, a picture of a stork. Is that a "stork" neuron? Maybe, but you can't be sure because you only tested 10 images. Perhaps an untested image makes that neuron respond even more. Widening your net to 100 images, you find that your neuron still responds to the stork, but it responds even more to the picture of an ostrich that is part of the new image collection. Does it mean your neuron is a bird neuron? How can you be sure? So, you test 1,000 images, it takes much longer to do the experiment, and this time an alpaca image happens to be the best driver of your neuron, even more than the two bird images. Does this mean you have an animal neuron? Or perhaps, your neuron responds only to long necks? This experiment can continue forever because there is an infinite number of possible images and features in the world, thus you can never be sure what drives your neuron most. Like Rumi's "elephant in the dark" parable, each test image reveals a part of the truth, but it can also mislead you away from the truth. The good news is that now, in a study published in the current issue of *Cell*, Ponce et al. (2019) might have cracked the problem.

One might ask, what is the use of discovering the best driver of an IT neuron? That is a legitimate question and we will get back to it, but this approach

has been very fruitful for understanding low-level visual processing. When Hubel and Wiesel (1959) discovered orientation-selective neurons in the primary visual cortex (V1), they struggled with the same problem. Although they recorded neural responses mostly to circles and lines, there still existed an infinite number of visual patterns that could—in theory—drive V1 cells even more. Development of spike-triggered averaging (STA) in 70 s and 80 s partially addressed this problem (Ringach and Shapley, 2004). STA is an unbiased method that uses visual noise—instead of showing all possible images—to estimate the visual pattern that drives a neuron most. Such visual patterns were referred to as "kernels." It turned out that Hubel and Wiesel were touching only the tusk of the elephant, as V1 kernels were not exactly "oriented bars," they looked more like oriented grating patches (Gabor filters) encoding spatial frequency as well as orientation. Discovery of V1 kernels was a major triumph for visual neuroscience because we now knew that the visual cortex uses a limited set of basis functions that can represent any image in V1 language, like a standard set of "letters" in an alphabet to express a visual sentence, making the raw image workable for further processing.

Machine City

Moving higher in the brain from V1 to IT, is there a visual alphabet for object recognition? How can we find the kernels of IT neurons? Unlike V1, the IT violates the assumption of linearity of the neural response required for STA. Thus, we need another systematic method for searching the very large space of possible complex visual patterns without human bias. In the absence of machine power, Tanaka's group developed a human-driven method called "reduction" for finding IT kernels (e.g., Kobatake and Tanaka, 1994). They first found a natural object that drove a given IT neuron, then manually varied the visual features of the object until they found the minimal necessary visual features that drove the neuron as well or more than the natural object. This was done in hope of discovering and cataloging the basis set of kernels that represent natural objects in IT cortex. As valuable as "reduction" studies were, the human factor involved in the process left it open to potential bias. Another strategy to reveal object kernels in an unbiased way uses simplified but parametrized images and moves the recording site to the earlier cortical area, V4 (e.g., Pasupathy and Connor, 2002); however, this approach comes with the cost of limiting the search to a small subspace of all possible images.

Now, almost two decades into the 21st century, Ponce et al. (2019) finally provides an exciting, unbiased machine-driven method for finding the kernels of IT neurons. Ponce et al. (2019) used a combination of genetic algorithms and deep generative networks to navigate in the nearly infinite space of images and arrive to an "evolved image" for each studied IT neuron. These computer-generated images drove IT neurons to very high rates (see Walker et al., 2018 for a similar methodology). The evolved images look quite counter-intuitive: some of the evolved kernels reveal strikingly detailed structures that resemble specific natural images, other kernels show complex structures that are hard to intuitively map to any natural structure. Neither case is consistent with the notion of an abstract limited alphabet of features as seen in V1 cortex. If there is an alphabet for object recognition, it looks more like hieroglyphs, a vast array of characters, each loaded with more information in comparison to the small yet universal set of letters in classical alphabets.

Remarkably, the "images" generated by Ponce and colleagues constitute a significant component of their results. Traditionally, images are taken as qualitative information, but this study demonstrates how modern computational power can generate and analyze complex images as quantitative information. This increases the dimensionality of the data and constrains the scientific hypotheses more strictly. For instance, now that some sophisticated models of object recognition exist (Yamins and DiCarlo, 2016), physiologically harvested IT kernels can be used to strictly constrain and improve computational models of information processing in IT cortex.

Energy Landscape

There is one problem with the notion of "kernel" in a high-level area like IT cortex, and that's—I suppose—why the authors have wisely (unlike the author of this preview) avoided this word in their paper and instead used the term "evolved image"; "kernel" implies specificity. For typical kernels defined in V1, we don't expect a neuron to be equally committed to multiple distinct kernels. For an IT "evolved image" we don't know whether it represents a global maximum in the space of images, something that is more kernel-like, or whether it is only a local maximum, one of the many local response peaks in a vast landscape of unrelated images. The observation that multiple independent evolutions can arrive at "similar" images for each neuron loosely supports the idea of a global maximum but without a study specifically tailored to address this problem, the results remain inconclusive. Both situations (having a global maximum or multiple local maxima) are informative for understanding how the brain processes complex information, but this important issue needs to be clarified by future studies before engaging such data in rigorous modeling.

There Is a Crack in Everything

An interesting aspect of the "evolution" method used in Ponce et al. (2019) is the adaptive nature of the paradigm. The image evolutions were optimized in this case for high neural firing, but the method could also be used to optimize for low firing or even discriminability of images for populations of IT neurons. Because of this adaptive nature, this method is a great tool for finding points of discrepancy between computational models of IT and real IT. Finding those cracks in the models will accelerate the process of model falsification and evolution. Independent of finding the flaws of computational models, this adaptive process can be used as a perfect adversarial tool to discover design cracks of IT cortex itself. What are the minimal image perturbations that make IT neurons fail to discriminate patterns? What are the image perturbations that make an object look like another to IT neurons? What do those images look like to the human eye? Ultimately, using this type of adaptive process to find a system's flaws can help with understanding it. As the poet Leonard Cohen writes, "There is a crack in everything. That's how the light gets in."

REFERENCES

Hubel, D.H., and Wiesel, T.N. (1959). Receptive fields of single neurones in the cat's striate cortex. J. Physiol. *148*, 574–591.

Kobatake, E., and Tanaka, K. (1994). Neuronal selectivities to complex object features in the ventral visual pathway of the macaque cerebral cortex. J. Neurophysiol. *71*, 856–867.

Pasupathy, A., and Connor, C.E. (2002). Population coding of shape in area V4. Nat. Neurosci. *5*, 1332–1338.

Ponce, C.R., Xiao, W., Schade, P.F., Hartmann, T.S., Kreiman, G., and Livingstone, M.S. (2019). Evolving images for visual neurons using a generative network reveals coding principles and neuronal preferences. Cell *177*, this issue, 999–1009.

Ringach, D., and Shapley, R. (2004). Reverse correlation in neurophysiology. Cogn. Sci. *28*, 147–166.

Walker, E.Y., Sinz, F.H., Froudarakis, E., Fahey, P.G., Muhammad, T., Ecker, A.S., Cobos, E., Reimer, J., Pitkow, X., and Tolias, A.S. (2018).https://www.biorxiv.org/content/10.1101/506956v1.

Yamins, D.L., and DiCarlo, J.J. (2016). Eight open questions in the computational modeling of higher sensory cortex. Curr. Opin. Neurobiol. *37*, 114–120.

Atlas Drugged

Jung-Kuei Chen[1] and Michael B. Yaffe[1,2,3,4,*]

[1]Center for Precision Cancer Medicine, David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

[2]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

[3]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

[4]Division of Surgical Critical Care and Trauma, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

*Correspondence: myaffe@mit.edu

https://doi.org/10.1016/j.cell.2019.04.023

Vasaikar et al. report a comprehensive proteogenomic analysis of 110 colon cancer samples to identify a variety of potential signaling and metabolic targets, neoantigens, and biomarkers. This resource helps expand our understanding of the fundamental pathophysiology of this tumor type, and future mechanistic studies should help guide novel therapeutic strategies for colon cancer treatment.

Colorectal cancers result from abnormal signaling events that arise within a defined landscape of mutations and genomic abnormalities (Vogelstein et al., 2013). Our understanding of these altered tumor genomes, and their corresponding RNA expression patterns, has accelerated dramatically with the advent of advanced sequencing technologies, in combination with novel methods for analysis of these massive datasets. This information has resulted in better characterization of specific tumor subtypes that arise within a particular organ (i.e., breast or colon) (Cancer Genome Atlas Network, 2012; Guinney et al., 2015); validated that the same basic set of oncogenes and signaling pathways that had been discovered in the pre-genomic era were, in fact, responsible for the vast majority of tumor types (Yaffe, 2013); and in some cases altered therapeutic decisions by identifying specific oncogenic mutations that strongly influence whether, at the population level, tumors are likely to respond to a particular drug or biological agent or not (Karapetis et al., 2008). Recent data, however, indicate that genomic and RNA expression data do not appear to be sufficient, on their own, to dictate the optimal choice of anti-cancer agents with which to treat a particular patient's tumor in most cases (Massard et al., 2017). Future advances in precision cancer medicine in the post-genomic era are therefore focusing on clarifying the biology of individual tumors by complementing genomic and RNA expression data with additional information about the tumor proteome and epigenome, and detailed analysis of post-translational modifications, in order to capture the signaling state of the cells within the tumor.

A major caveat in the use of traditional mass-spectrometry-based proteomics for the analysis of individual patient tumors is that proteins are typically identified and quantified by matching peptides detected in the mass spectrometer to those present in a reference database such as Ensembl and RefSeq. Consequently, it is not possible to identify novel cancer-specific proteins with this approach. Proteogenomics, a combination of genomics and proteomics, attempts to overcome this problem by using genomic information including whole-exome and RNA sequencing (RNA-seq) of a particular patient's tumor to generate a customized reference protein sequence database, allowing the identification of novel cancer-specific peptides and protein variations (Nesvizhskii, 2014) within a patient-specific tumor "atlas."

The first large-scale proteogenomic analysis of colorectal cancer was conducted by the NCI-CPTAC group in 2014 (Zhang et al., 2014), in which 95 patient tumors that had previously been sequenced as part of the Cancer Genome Atlas (TCGA) were subsequently analyzed by liquid chromatography-tandem mass