π = Visual Cortex

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full genome sequences in the mid-1990s led to the construction of genome-scale metabolic models that were able to recapitulate optimal growth phenotypes (*6*). The reconstruction of the entire protein synthesis machinery (*7*) moved us up a notch in the hierarchy, enabling the description of the optimal ribosomal content as a function of growth rate (the starting point for Scott *et al.*). At the systems biology level, "omics" data sets have led to an understanding of how optimal network properties form (*8*, *9*). At this level, a combination of inference methods (*10*) and bottom-up reconstructions has proved productive (*11*). Decomposing network functionality into coordinately expressed gene clusters, and determining the degree of flexibility within and among these clusters (in terms of expression levels), could complete our understanding of the hierarchy, now that we have the top-level relationships developed by Scott *et al.*

Taken together, these developments lead to a multiscale understanding of the genotype-phenotype relationships underlying metabolism and growth in microbes. At all levels, model structures must be developed in order to adequately capture constraints and allow for optimization subject to these constraints (*12*). Cementing these levels into a coherent multiscale framework is a challenge facing the field. Experiments that enable bacteria to rapidly evolve in controlled laboratory settings are a way to interrogate this relationship further, as they produce optimal growth phenotypes (*13*, *14*). The genetic basis for such changes in phenotype can now be determined through whole-genome resequencing, followed by allelic replacement to identify causal mutations (*15*). Clearly, an exciting era is ahead of us, in which a combination of in silico and experimental approaches promises to continue the development of mechanistic and principled genotype-phenotype relationships that are akin to the development of fundamental physical laws a century ago. If successful, such development will move microbiology into a fundamentally new realm.

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NEUROSCIENCE

π = Visual Cortex

Three distantly-related mammals share a brain architecture characterized by a density of π

Kenneth D. Miller

Archimedes, the great scientist of ancient Greece, performed the first systematic calculation of the value of π, the ratio of a circle's circumference to its diameter. Twenty-three centuries later, scientists continue to be delighted by π's appearance in new and unexpected areas of science. The latest is perhaps the most surprising: On page 1113 of this issue, Kaschube *et al.* (*1*) show that three distantly-related mammals share a common organizing scheme for neurons in the brain's visual cortex characterized by a density closely approaching 3.14 (π). The result offers insight into the development and evolution of the visual cortex, and strongly suggests that key architectural features are self-organized rather than genetically hard-wired.

The cerebral cortex is a thin, six-layer sheet of neurons. A long-standing model system for cortical studies is the primary visual cortex (V1), the first piece of cortex to receive visual input (*2*). Neurons in V1 are highly selective for the spatial orientation of a light/dark edge; some prefer (respond best to) vertical edges, whereas others prefer horizontal or diagonal lines. Preferred orientation exhibits what is called "columnar" organization: The neurons beneath any given spot on the cortical sheet, across the layers, prefer the same orientation. Imaging techniques allow researchers to visualize the arrangement, or "map," of preferred orientations across the cortical sheet (see the figure). These orientation maps have a quasi-periodic structure: Preferred orientations change continuously across the sheet, repeating every millimeter or so. The local distance between repeats is the local "map period" (λ). The maps also contain "pinwheels"— points at which all preferred orientations converge. There has long been debate over the degree to which these features reflect detailed genetic programming or self-organization based on general rules that guide the growth and decay of synapses (*3*, *4*).

To explore this question, Kaschube *et al.* compared, with unprecedented quantitative precision, the density and arrangement of pinwheels in three mammals: the galago, a primate; a tree shrew, a close primate relative; and a distantly related carnivore, the ferret. This precise measurement of pinwheel distribution required considerable advances. Measurement "noise" corrupts maps, and existing methods to "smooth" the noise also smooth away, or hide, real pinwheels. The authors found filters that solve this problem. They also used wavelet-based methods that they had previously developed to precisely measure the local map period (*5*), and they gained precision by analyzing an unprecedented number of maps (more than 100) and pinwheels (roughly 10,000).

They found strong evidence of a common design. Most strikingly, the mean density of pinwheels per λ^2 was within 1% of π for all three species. The grand average was 3.14, with a 95% confidence interval of 3.08 to 3.20 (π ± 2%). Does a density of π just follow from the periodic map structure? To test this, they "phase-randomized" measured maps, creating maps that precisely retained the measured periodic structure but were otherwise random (see the figure). These maps had much higher pinwheel densities (mean 3.50), which suggests that π is a special property of the maps found in brains.

Why should the pinwheel density be π? Kaschube *et al.* have a beautiful theoretical answer. For many years, the senior author, Fred Wolf, and his group have been constructing a theory of orientation map development that builds on mathematical methods devel-

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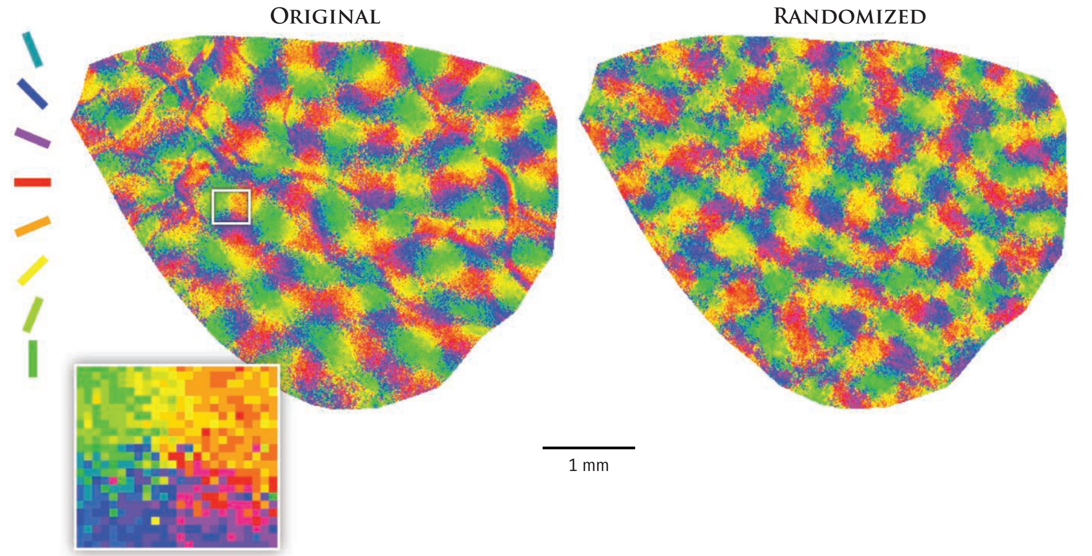

Pinwheels and π. Colors on an orientation map from a galago visual cortex (**left**) indicate preferred orientations of neurons (lines, far left). Orientations change roughly periodically, cycling from red to red with fairly regular spacing. (Colored lines across the map are blood vessel artifacts.) Pinwheels (inset) form where all orientations meet. Real maps have mean pinwheel density close to π. A phase randomized version of the same map (**right**) has a higher density, suggesting that a pinwheel density approaching π is a self-organized feature of the visual cortex.

oped in physics for studying pattern formation (*6*). These methods allow division of models into "universality classes," such that all models in a class share the same set of possible outcomes (e.g., the same set of possible orientation maps) when a certain "control parameter" is small. Wolf and his colleagues assumed, as in many previous models of orientation maps (*7*), that each site in the two-dimensional cortical sheet is characterized by two variables: an orientation preference and selectivity. These variables then develop through mutual interactions; for example, a site preferring vertical might nudge its neighbors toward the same preference. They assumed that these interactions respect basic symmetries; for example, the interactions between a site and its surrounding sites should have the same form no matter where the site is on the cortical sheet. Finally, they allowed for long-range interactions (between sites more than a map period apart), based on the presence in V1 of long-range connections between neurons. In the mature animal, these connections link cells of similar preferred orientation (*8*), and their basic structure is present before orientation maps develop (*9*, *10*). They showed that all models that share the basic symmetries they assumed, and also have long-range suppressive interactions, form a universality class that generates maps with pinwheel densities closely approaching π (*11*). ["Suppressive" means that a site preferring vertical tends to push connected sites away from vertical; this is consistent with the largely suppressive effects that V1's long-range connections have on neural activity (*8*).] The suppressive long-range interactions are key to stabilizing pinwheels, which otherwise largely disappear during development. The theoretical framework strictly applies only when the control parameter is small, but in numerical simulations of a particular biologically plausible model in the class, Kaschube *et al.* found that the conclusions apply more broadly. Thus, a large and very plausible class of self-organizing models predict—independent of model details and with no tunable parameters—the precise structures that Kaschube *et al.* found across distant species.

The universality of self-organizing behavior provides a simple and compelling explanation for the arrival of widely divergent evolutionary lines at this common design. Rodents and lagomorphs, which separated from the primate/shrew line long after carnivores, lack orientation maps (their V1 neurons are orientation selective, but preferred orientation varies apparently randomly from cell to cell) (*12*–*14*). Thus, maps either independently evolved at least twice, or arose once and were lost in the rodent/lagomorph lines. The common ancestor of primates and carnivores had small brains with little neocortex (*15*). If this ancestor's V1 had maps, they likely would have contained only a small number of "hypercolumns" (regions of area λ^2). How did the common design either evolve twice, or persist in distant lines through substantial changes in V1, including an expansion to hundreds or thousands of hypercolumns? The universality of self-organization provides a simple answer; it is very difficult to think of a plausible alternative.

There is still much to be determined. This theoretical framework applies to maps containing power (a measure of signal strength) at only a single spatial period, and must be extended to incorporate the fact that real maps contain power over a broader range of periods. In addition, circuit development is determined by rules governing the growth and decay of thousands of synapses impinging on each neuron. How does this complexity yield a high-level description in terms of interactions between just two variables per cell (orientation preference and selectivity)? Experimentally, it will be fascinating to fill in the evolutionary tree of orientation maps and the common design. A definitive experiment, not yet technically feasible, would be to specifically eliminate the long-range connections during brain development and see whether maps with low pinwheel density develop, as theory predicts. Despite some caveats, the parameter-free prediction of π and its experimental verification to 2% precision will stand as landmarks of theoretical biology, as well as tremendous spurs to our thinking about cortical evolution and development.

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