

tion processing task such as filtering out spurious input fluctuation (25), generating temporal programs of expression (3, 25) or accelerating the throughput of the network (2, 26). Recently, the same network motifs were also found in the transcription network of yeast (7, 27). It is important to stress that the similarity in circuit structure does not necessarily stem from circuit duplication. Evolution, by constant tinkering, appears to converge again and again on these circuit patterns in different nonhomologous systems (25, 27, 28), presumably because they carry out key functions (see Perspective (29) STKE). Network motifs can be detected by algorithms that compare the patterns found in the biological network to those found in suitably randomized networks (25, 27). This is analogous to detection of sequence motifs as recurring sequences that are very rare in random sequences.

Network motifs are likely to be also found on the level of protein signaling networks (30). Once a dictionary of network motifs and their functions is established, one could envision researchers detecting network motifs in new networks just as protein domains are currently detected in the sequences of new genes. Finding a sequence motif (e.g., a kinase domain) in a new protein sheds light on its biochemical function; similarly, finding a network motif in a new network may help explain what systems-level function the network performs, and how it performs it.

Will a complete description of the biological networks of an entire cell ever be available? The task of mapping an unknown network is known as reverse-engineering (3, 31–33). Much of engineering is actually reverse-

engineering, because prototypes often do not work and need to be understood in order to correct their design. The program of molecular biology is reverse-engineering on a grand scale. Reverse engineering a nonmodular network of a few thousand components and their nonlinear interactions is impossible (exponentially hard with the number of nodes). However, the special features of biological networks discussed here give hope that biological networks are structures that human beings can understand. Modularity, for example, is at the root of the success of gene functional assignment by expression correlations (11, 34). Robustness to component tolerances limits the range of possible circuits that function on paper to only a few designs that can work in the cell. This can help theorists to home in on the correct design with limited data (21–23). Network motifs define the few basic patterns that recur in a network and, in principle, can provide specific experimental guidelines to determine whether they exist in a given system (25). These concepts, together with the current technological revolution in biology, may eventually allow characterization and understanding of cell-wide networks, with great benefit to medicine. The similarity between the creations of tinkerer and engineer also raises a fundamental scientific challenge: understanding the laws of nature that unite evolved and designed systems.

References and Notes

1. F. Jacob, *Science* **196**, 1161 (1977).
2. M. Savageau, *Biochemical Systems Analysis: A Study of Function and Design in Molecular Biology* (Addison-Wesley, Reading, MA, 1976).
3. M. Ronen, R. Rosenberg, B. I. Shraiman, U. Alon, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 10555 (2002).
4. C. H. Yuh, H. Bolouri, E. H. Davidson, *Science* **279**, 1896 (1998).

5. Y. Setty, A. E. Mayo, M. G. Surette, U. Alon, *Proc. Natl. Acad. Sci. U.S.A.* **100**, 7702 (2003).
6. D. Thieffry, A. M. Huerta, E. Perez-Rueda, J. Collado-Vides, *Bioessays* **20**, 433 (1998).
7. T. I. Lee et al., *Science* **298**, 799 (2002).
8. E. H. Davidson et al., *Science* **295**, 1669 (2002).
9. S. H. Strogatz, *Nature* **410**, 268 (2001).
10. L. H. Hartwell, J. J. Hopfield, S. Leibler, A. W. Murray, *Nature* **402**, C47 (1999).
11. J. Ihmels et al., *Nature Genet.* **31**, 370 (Aug. 2002).
12. E. Ravasz, A. L. Somera, D. A. Mongru, Z. N. Oltvai, A.-L. Barabási, *Science* **297**, 1551 (2002).
13. C. R. Myers, arXiv: cond-mat/0305575 (2003).
14. J. J. Hopfield, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 2554 (1982).
15. D. Bray, *J. Theor. Biol.* **143**, 215 (1990).
16. H. Lipson, J. B. Pollack, N. P. Suh, *Evolution* **56**, 1549 (2002).
17. J. Gerhart, M. W. Kirschner, *Cells, Embryos, and Evolution: Toward a Cellular and Developmental Understanding of Phenotypic Variation and Evolutionary Adaptability* (Blackwell Science Inc, Oxford, 1997).
18. C. H. Waddington, *Nature* **150**, 563 (1942).
19. H. Kacser, J. A. Burns, *Symp. Soc. Exp. Biol.* **32**, 65 (1973).
20. M. Savageau, *Nature* **229**, 542 (1971).
21. N. Barkai, S. Leibler, *Nature* **387**, 913 (1997).
22. U. Alon, M. G. Surette, N. Barkai, S. Leibler, *Nature* **397**, 168 (1999).
23. A. Eldar et al., *Nature* **419**, 304 (2002).
24. D. Fell, *Understanding the Control of Metabolism* (Portland Press, London, 1997).
25. S. S. Shen-Orr, R. Milo, S. Mangan, U. Alon, *Nature Genet.* **31**, 64 (2002).
26. N. Rosenfeld, M. B. Elowitz, U. Alon, *J. Mol. Biol.* **323**, 785 (2002).
27. R. Milo et al., *Science* **298**, 824 (2002).
28. G. C. Conant, A. Wagner, *Nature Genet.* **34**, 264 (2003).
29. A. Wagner, *Sci. STKE* **2003**, pe41 (2003).
30. C. V. Rao, A. P. Arkin, *Annu. Rev. Biomed. Eng.* **3**, 391 (2001).
31. M. E. Csete, J. C. Doyle, *Science* **295**, 1664 (2002).
32. A. Arkin, P. Shen, J. Ross, *Science* **277**, 1275 (1997).
33. T. S. Gardner, D. di Bernardo, D. Lorenz, J. J. Collins, *Science* **301**, 102 (2003).
34. M. B. Eisen, P. T. Spellman, P. O. Brown, D. Botstein, *Proc. Natl. Acad. Sci. U.S.A.* **95**, 14863 (1998).

VIEWPOINT

Social Insect Networks

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Social insect colonies have many of the properties of adaptive networks. The simple rules governing how local interactions among individuals translate into group behaviors are found across social groups, giving social insects the potential to have a profound impact on our understanding of the interplay between network dynamics and social evolution.

The formal exploration of social insect colonies as networks is in its infancy. However, social insects such as wasps, ants, and honeybees provide a powerful system for examining how network dynamics contribute to the evolution of complex biological systems. Social insect colonies (and social

groups generally) have key network attributes that appear consistently in complex biological systems, from molecules through ecosystems; these include nonrandom systems of connectivity and the self-organization of group-level phenotypes (1–3). Colonies exhibit multiple levels of organization, yet it is still possible to track individuals, making these societies more accessible to experimental manipulation than many other complex systems.

How can viewing insect societies as networks shape our understanding of social organization and evolution? First, they have become one of the central model systems for exploring self-organization: the process by which interactions occurring locally between individuals produce group-level attributes. Self-organization in a social insect colony produces emergent properties: social phenotypes that are greater than a simple summation of individual worker behaviors (2). The basic rules generating these dynamics are broadly applicable across taxa whose members show social behavior, and they produce ubiquitous patterns of social organization, including mass action responses, division of labor, and social hierarchies (2, 4).

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Second, the social insects provide an opportunity to explore how behavior evolves within complex systems. This has led to a shift in focus from variation among individuals to how interactions among individuals and groups shape that variation. Most of the well-studied social insects are eusocial (only one or a few individuals in the colony reproduce), and the colony is considered an adaptive unit made up of related individuals (5). Because of this, we are comfortable in relating group dynamics to fitness effects at both the individual and group levels. However, multilevel selection acts on social insect colonies, not just because their members are highly related but also because they are densely connected networks. This emerging view of social groups as networks contributes to a growing awareness of how the fitness of individuals and groups is generated interactively across levels of biological organization (3, 6, 7).

To explore the relationships between complexity and selection in social systems, we first need to describe the social group as a network. A network is simplistically a system of interacting elements, or nodes, that communicate with each other [see (8, 9) in this issue]. Social insect colonies are dense networks in which individuals have multiple points of contact (1, 10). As dense networks, colonies distribute information rapidly, allowing them to respond flexibly and efficiently to the dynamic environment in which they live. An extreme example is the alarm response of African honeybees, in which an initial release of alarm pheromone by a few guards cascades within a minute to stinging responses by thousands of bees.

Like many biological systems, social insect colonies are also distributed networks (2). Although the colony generally has a single queen, she does not centrally control colony function. Instead, workers make decisions based on local information and perform behaviors in parallel (10). This is the case, to some degree, even for hierarchical systems such as the wasp network, where the queen controls the reproductive output of the colony but does not individually direct many aspects of day-to-day colony function. We lack sufficient data to accurately characterize the connections that occur between any two individuals within a colony, much less the connections across the society. However, it is clear that connections among nestmates are nonrandomly distributed for many, if not most, colony functions. A few key individuals, or hubs, distribute information (connect) to many

more nestmates than do others. The most obvious of these is the queen, who, in honeybees, secretes a pheromone that represses reproduction in workers and maintains colony cohesion. Queen pheromone is transmitted to workers as they groom her, then is rapidly transmitted through the hive via trophallaxis and deposits on nest wax (11). Key individuals are also present within worker task groups, where they stimulate performance of a task or provide a central point around which performance is organized (12). For example, foraging task groups often include scouts or dancers. They communicate most of the information about resource location and availability and, in ants, often maintain the cohesion of groups of recruits that go out to forage (10, 12, 13).

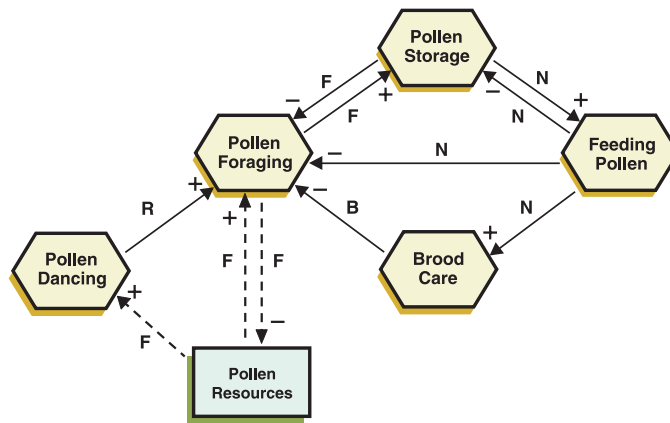


Fig. 1. The network pathways modulating pollen foraging in a honeybee colony (developed with T. Taylor). Nodes are the tasks linked to pollen foraging; vectors are the individuals transmitting information: F, forager; N, nurse; B, brood; R, recruit. Foragers returning with pollen receive information about pollen storage levels as they place pollen loads into cells. The amount of stored pollen is negative feedback for pollen foraging. Pollen is removed from cells by nurse bees, who feed it first to developing brood and give excess to pollen foragers. Receiving pollen from nurses is negative feedback for foraging. Foragers also receive information about pollen stores from brood, who produce a hunger pheromone when they are not fed; brood care reduces hunger levels. Information on pollen availability and location is transmitted by pollen dancers. Dancing elicits recruitment to foraging by workers not actively engaged in foraging (2, 20–22).

The importance of these rare individuals makes it likely that for many functions the colony network becomes scale-free, which means that variation in connectivity is best described by a power law rather than a Poisson distribution (14). This is important to colony resiliency, because it means that the loss of any of the vast majority of workers would have little effect. In contrast, removing nodes within a randomly distributed network can quickly fragment the system. Although scale-free networks are buffered from the effects of random loss, the removal of key nodes can severely disrupt the system (1, 14). The colony has long-term mechanisms to replace any element, including the queen, but the removal of key individuals does have immediate disruptive effects. Loss of

the scout who discovers a foraging trail can completely block the retrieval of a resource, yet removing the recruits who follow the scout has little effect on overall foraging (15). Social insect networks are similar in this way to other biological networks, from food webs with keystone species (16) to metabolic pathways, in which a few key molecules are involved in most reactions (9, 17).

With these global attributes in place, how does information transfer within a social colony actually occur? Unfortunately, we do not yet have enough empirical data to answer this question well. Models to date have explored networks in the context of task regulation: the amount of effort by individuals or groups that is allocated to different tasks. One approach has been to consider the colony as a regular network (9), in which individuals performing the same task form clusters of high connectivity, with weaker links across tasks (18, 19). In a model of recruitment to alternate resource pathways, Bonabeau *et al.* (19) showed that colonies can balance efficient utilization of a single resource with flexible allocation across resources by a mixed strategy of within-cluster information transfer coupled with global information transfer across clusters. An important finding of this model [and the Pacala *et al.* model (18) on which it was based] is the importance of cross-cluster links in maintaining flexibility for moving individuals from one task or cluster to another.

The assumptions of the Bonabeau *et al.* model (19) fit well into the context of trail selection during foraging, where the signals are well defined. However, expanding the model more widely to multiple tasks has been problematic. One reason is that contacts between workers are extremely fluid. Connections between workers in a social insect colony are ephemeral, and signals themselves can outlive connections. Signal systems are also highly diverse in information content and include large-scale signals, such as alarm pheromones, that target the colony globally (10).

Social insect networks are traditionally modeled with workers as nodes. However, because worker interactions are so fluid, we can alternatively map the system from the perspective of treating tasks as nodes and individual workers as connectors (symbolic dynamics). Figure 1 describes such a map for the short-term modulation of pollen foraging in honeybees. It is clear from this map that

cross-task connections are the primary pathways for regulating pollen foraging. Pollen foraging is homeostatically regulated around pollen storage levels and is positively regulated around brood, for which it is the main nutrient source (20). Pollen foragers collect most of their information about colony pollen need and/or intake either indirectly via changes in pollen stores, from nurse bees who feed foragers when excess pollen is available, or from brood who emit hunger signals (21, 22). The map is not consistent with the assumption of high within-cluster connectivity, but it does support the assertion that connections across tasks are important to allocation (18, 19). They may, in fact, be the primary links modulating task regulation globally. If so, information flow in social insect colonies has an important similarity to that in human social networks, where weak ties across social clusters play an important role in regulating society as a large-scale network (23).

Although the complexities of the whole-colony network have not yet been well described, large strides have been made in the analysis of how local interactions within the network affect global colony dynamics. As dense networks, social insect colonies have a high potential for the emergence of large-scale phenomena via self-organization (1). Self-organization pervades all aspects of colony function, including foraging, nest defense, resource storage, nest construction, site selection, thermoregulation, and division of labor (2).

The growing body of theoretical and empirical work on self-organization is one of the more important contributions of social insect research to understanding biocomplexity (2). What is perhaps most important about self-organization in social insects is that it is not based on derived characteristics unique to the taxon. Instead, it is driven by a limited set of nonlinear dynamics that should occur across social systems, from insects to humans (2, 4). As an example, a majority of the emergent components of social behavior can be categorized as “convergent,” in which individuals become behaviorally more similar, or “divergent,” in which the behavior of one individual reduces the likelihood that the second individual will perform the same behavior.

The minimal components (or minimal rule set) for convergence can be condensed to (i) a positive stimulus for the behavior as a result of its performance; (ii) amplification of the stimulus through successive iterations; and (iii) a decay component, so that signals and cues must be regenerated. A beautiful example of behavioral convergence via these minimal rules is found in the trail marking system of the Argentine ant *Linepithema humile*. Workers traveling to and from resources lay a pheromonal trail. Each time a trail is laid, the local

environment at points of choice between alternate trails is changed. Ants reaching these points preferentially choose the trail with more pheromone and add to it, creating a positive feedback loop. Meanwhile, the pheromone marks on the alternate trail decay. As more foragers repeat this process, one trail becomes the primary and often the only route (2, 24). These simple rules underlie trail-making in multiple ant species (2). Similar rules describe convergent group behaviors in other social species, such as migrating social spiders who choose a direction of travel based on the accumulation of draglines from others in the group (25).

The minimal rule set for divergence can be condensed to two components: (i) performance of a behavior by one individual reduces the probability that others will perform the same behavior, and (ii) stimulus levels for the behavior increase in the absence of performance. Most divergence models also include a positive feedback loop, in which performance of the behavior increases the probability that the individual will perform the behavior again. This self-reinforcement generates divergence even with initially small random differences in behavior and produces a faster and more stable system of divergence (26). However, divergence can emerge in the absence of self-reinforcement if individuals initially differ intrinsically in their response thresholds: the stimulus level at which they respond by performing a behavior (27, 28).

This rule set forms the basis for the response threshold models of division of labor (27). These models begin with the initial assumption that individuals perform a task when environmental stimuli reach a level that matches the individual's threshold for response. That individual performs the task; in doing so, she reduces the stimulus levels encountered by others and thus reduces their probability of performing the task also. Empirical tests on solitary bees and on ant queens during colony founding have shown that division of labor can emerge even without a history of direct selection (29). When normally solitary ant queens are forced into artificial social groups, one individual takes over the task of excavation, whereas the other individual remains in the nest and tends brood. The dynamics of this division of labor fit well with the predictions of the response threshold model.

Similar patterns of divergence occur across other social taxa. Social hierarchies within bumblebees and primates can be modeled by a similar minimal rule set for divergence, coupled with reinforcement (30, 31). Division of labor also appears frequently within social species, including humans. As an example, we can imagine an apartment where housemates share

tasks. Used dishes pile up in the sink, producing a continuously increasing stimulus. The dishes go unnoticed until the threshold of the one most sensitive to them is met, and he or she washes them. This removes the dishes as a stimulus, further reducing the likelihood that the other group members will ever wash them. The result is a dishwashing specialist (much to his/her dismay), and a set of nondishwashers. Similar interactions across other chores, from cleaning the bathroom to taking out the garbage, generate a division of labor for the household.

The realization that individuals within a social group are linked as a network is important to our understanding of how selection acts on sociality. The fitness of every individual in the group is produced in part as a result of their interactions with other group members. The emergence of collective behaviors via self-organization also produces phenotypes at the colony level that are themselves subject to selection (7). These interactions set the stage for multilevel selection (32). Network-level properties, including group size, connectivity, and even variation in individual responsiveness to signals can all shape the adaptive function of the social group (18, 28). As an example, as described above, the emergence of division of labor is based in part on intrinsic variation in worker response thresholds. Honeybee colonies with more diversity in worker thresholds for foraging are able to respond better to changes in the availability and need for resources. This diversity is generated by the extreme polyandry of honeybee queens, who mate with a dozen or more males (22).

Network interactions also have a profound influence on individual behavior and fitness. The fitness of each individual in a social group is dependent on the phenotypes of the other group members (7); they are each other's social environments. These reciprocal fitness effects are generated by nonlinear interactions within the social network. In some systems, self-organization can actually generate conflicting fitness effects at the individual and group levels. For ant queens, when division of labor spontaneously emerges from small initial differences in behavior (29), it produces associated fitness disparities, because the queen who takes over the task of nest excavation is more likely to die. Whether an individual becomes the excavator, and suffers the associated fitness consequences, depends on which group they land in and the thresholds of everyone in that group.

What should be done next in the exploration of social groups as networks? We need to expand our models from elegant descriptions of single behaviors to incorporate the more complex dynamics of the group as a whole. We also need to test those models empirically

on a wider range of social systems. Finally, to understand the evolutionary significance of network dynamics, we must explicitly measure their fitness effects on the social group (7). This interplay between network dynamics and selection is just beginning to be explored, and social insects have the potential to be on the leading edge.

References

1. A.-L. Barabási, *Linked: The New Science of Networks* (Perseus, Cambridge, MA, 2002).
2. S. Camazine et al., *Self-Organization in Biological Systems* (Princeton Univ. Press, Princeton, NJ, 2001).
3. R. Solé, B. C. Goodwin, *Signs of Life: How Complexity Pervades Biology* (Basic Books, New York, 2000).
4. C. K. Hemelrijk, *Ethology* **108**, 655 (2002).
5. T. D. Seeley, *Am. Nat.* **150**, S22 (1997).
6. D. S. Wilson, L. A. Dugatkin, *Am. Nat.* **149**, 336 (1997).
7. A. J. Moore, E. D. Brodie, J. B. Wolf, *Evolution* **51**, 1352 (1997).
8. U. Alon, *Science* **301**, 1866 (2003).
9. D. Bray, *Science* **301**, 1864 (2003).
10. B. Hölldobler, E. O. Wilson, *The Ants* (Belknap Press of Harvard Univ. Press, Cambridge, MA, 1990).
11. K. Naumann, M. Winston, K. Slessor, G. Prestwich, F. Webster, *Behav. Ecol. Sociobiol.* **29**, 321 (1991).
12. S. K. Robson, J. F. A. Traniello, in *Information Processing in Social Insects*, C. Detrain, J. L. Deneubourg, J. M. Pasteels, Eds. (Birkhauser, Basel, Switzerland, 1999), pp. 239–259.
13. T. D. Seeley, S. Camazine, J. Sneyd, *Behav. Ecol. Sociobiol.* **28**, 277 (1991).
14. R. Albert, A.-L. Barabási, *Rev. Mod. Phys.* **74**, 47 (2002).
15. D. M. Gordon, *Am. Nat.* **159**, 509 (2002).
16. R. Sole, J. Montoya, *Santa Fe Working Paper* 00-11-060 (2000).
17. H. Jeong, B. Tombor, R. Albert, Z. Oltvai, A.-L. Barabási, *Nature* **407**, 651 (2000).
18. S. W. Pacala, D. M. Gordon, H. C. J. Godfray, *Evol. Ecol.* **10**, 127 (1996).
19. E. Bonabeau, G. Theraulaz, J.-L. Deneubourg, *J. Theor. Biol.* **195**, 157 (1998).
20. J. H. Fewell, M. Winston, *Behav. Ecol. Sociobiol.* **30**, 387 (1992).
21. S. Camazine, *Behav. Ecol. Sociobiol.* **32**, 265 (1993).
22. R. E. Page, J. Erber, *Naturwissenschaften* **89**, 91 (2002).
23. M. Granovetter, *Am. J. Sociol.* **78**, 1360 (1973).
24. S. Goss, S. Aron, J. L. Deneubourg, J. M. Pasteels, *Naturwissenschaften* **76**, 579 (1989).
25. F. Saffre, R. Furey, B. Krafft, J. L. Deneubourg, *J. Theor. Biol.* **198**, 507 (1999).
26. G. Theraulaz, E. Bonabeau, J. L. Deneubourg, *Proc. R. Soc. London Ser. B* **265**, 327 (1998).
27. S. N. Beshers, J. H. Fewell, *Annu. Rev. Entomol.* **46**, 413 (2001).
28. R. E. Page, S. D. Mitchell, *Apidologie* **29**, 171 (1998).
29. J. H. Fewell, R. E. Page, *Evol. Ecol. Res.* **1**, 537 (1999).
30. P. Hogeweg, B. Hesper, *Behav. Ecol. Sociobiol.* **12**, 271 (1983).
31. C. K. Hemelrijk, *Biol. Bull.* **202**, 283 (2002).
32. D. S. Wilson, *Am. Nat.* **150**, S1 (1997).

REVIEW

Communication in Neuronal Networks

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Brains perform with remarkable efficiency, are capable of prodigious computation, and are marvels of communication. We are beginning to understand some of the geometric, biophysical, and energy constraints that have governed the evolution of cortical networks. To operate efficiently within these constraints, nature has optimized the structure and function of cortical networks with design principles similar to those used in electronic networks. The brain also exploits the adaptability of biological systems to reconfigure in response to changing needs.

Neuronal networks have been extensively studied as computational systems, but they also serve as communications networks in transferring large amounts of information between brain areas. Recent work suggests that their structure and function are governed by basic principles of resource allocation and constraint minimization, and that some of these principles are shared with human-made electronic devices and communications networks. The discovery that neuronal networks follow simple design rules resembling those found in other networks is striking because nervous systems have many unique properties.

To generate complicated patterns of behavior, nervous systems have evolved prodigious abilities to process information. Evolution has made use of the rich molecular repertoire, versatility, and adaptability of cells. Neurons can receive and deliver signals at up to 10^5

synapses and can combine and process synaptic inputs, both linearly and nonlinearly, to implement a rich repertoire of operations that process information (*I*). Neurons can also establish and change their connections and vary their signaling properties according to a variety of rules. Because many of these changes are driven by spatial and temporal patterns of neural signals, neuronal networks can adapt to circumstances, self-assemble, autocalibrate, and store information by changing their properties according to experience.

The simple design rules improve efficiency by reducing (and in some cases minimizing) the resources required to implement a given task. It should come as no surprise that brains have evolved to operate efficiently. Economy and efficiency are guiding principles in physiology that explain, for example, the way in which the lungs, the circulation, and the mitochondria are matched and co-regulated to supply energy to muscles (2). To identify and explain efficient design, it is necessary to derive and apply the structural and physicochemical relationships that connect resource use to performance. We consider first a number of studies of the geometrical constraints on packing and wiring that show that the brain is organized to reduce

wiring costs. We then examine a constraint that impinges on all aspects of neural function but has only recently become apparent—energy consumption. Next we look at energy-efficient neural codes that reduce signal traffic by exploiting the relationships that govern the representational capacity of neurons. We end with a brief discussion on how synaptic plasticity may reconfigure the cortical network on a wide range of time scales.

Geometrical and Biophysical Constraints on Wiring

Reducing the size of an organ, such as the brain, while maintaining adequate function is usually beneficial. A smaller brain requires fewer materials and less energy for construction and maintenance, lighter skeletal elements and muscles for support, and less energy for carriage. The size of a nervous system can be reduced by reducing the number of neurons required for adequate function, by reducing the average size of neurons, or by laying out neurons so as to reduce the lengths of their connections. The design principles governing economical layout have received the most attention.

Just like the wires connecting components in electronic chips, the connections between neurons occupy a substantial fraction of the total volume, and the wires (axons and dendrites) are expensive to operate because they dissipate energy during signaling. Nature has an important advantage over electronic circuits because components are connected by wires in three-dimensional (3D) space, whereas even the most advanced VLSI (very large scale integra-

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