positions, which determine the composition of local communities. Perhaps an even more fundamental element in Maurer's model is its assumption about the positive relationship between range size and average local density.

Macroecology emerged to challenge an approach to community ecology obsessed with experiments and conducted at a small spatial scale in simplified communities. Whatever you call the macroscopic perspective Maurer advocates, we need to document large-scale ecological patterns. We need to retain the broader ecological contexts of local communities and to understand how regional processes influence them. Disentangling ecological complexity is a vast task in which many approaches are required. Whether the one that Maurer provides will help us meet our unresolved challenges remains to be seen.

References

1. T. H. Fritts and G. H. Rodda, *Annu. Rev. Ecol. Syst.* **29**, 113 (1998).
2. I. Hanski and H. Henttonen, *J. Anim. Ecol.* **65**, 220 (1996).
3. J. H. Brown and B. A. Maurer, *Science* **243**, 1145 (1989).
4. R. M. May, *Stability and Complexity in Model Ecosystems* (Princeton Univ. Press, Princeton, NJ, 1973).

PERSPECTIVES: NEUROBIOLOGY

Dissecting Dendrite Dynamics

Stephen J. Smith

The functioning of the brain depends on the interconnections of billions of neurons through trillions of synapses. But what developmental processes could possibly guide the correct formation of such vast numbers of synaptic connections? This question is at the heart of understanding brain development and the storage and processing of information throughout life. Although the surface of this problem has barely been scratched, some of the scratches have become a little deeper with new observations by Maletic-Savatic and colleagues reported on page 1923 of this issue (*1*). A confluence of new optical imaging methods enabled these investigators to take a much closer look at the dynamics of neuronal structure in developing brain tissue. They conclude that patterns of electrical activity may shape the morphology of developing neurons by promoting new dendritic extensions called filopodia, which may in turn initiate the formation of new synapses (synaptogenesis). The authors go on to show that activation of the *N*-methyl-D-aspartate (NMDA) receptor by electrical activity may be the event that triggers filopodial extension and synapse formation.

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Two decades of experiments have demonstrated that the electrical activity of neurons can shape patterns of synaptic interconnections during early development (*2*). For instance, nerve impulses in the pathways that carry sensory information influence the functional maps of the brain areas that receive these impulses. But it is not just the total number of impulses that count; temporal or spatial patterning of impulse activity may critically influence the shaping of such brain maps. The formation of memory in the mature brain also may involve activity-dependent morphological changes in neurons similar to those seen in early development (*3*). Although there are numerous well-documented examples of electrical activity driving neuronal morphogenesis, there have been few clues to indicate how this comes about.

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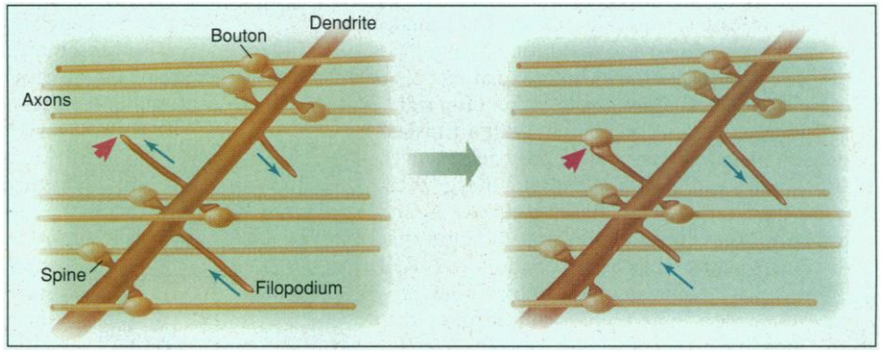
One molecular lead implicates the NMDA receptor, which binds the neurotransmitter glutamate at excitatory synapses in the central nervous system (*4*). Compared to other types of glutamate receptor found at excitatory synapses, the NMDA receptor plays a minor role in generating postsynaptic electrical responses. Rather, upon activation by glutamate, the NMDA receptor promotes a local influx of calcium ions (*5*). The effects of NMDA receptor activation are thus much more localized than those of other glutamate receptors whose electrical signals are conducted over much greater distances. Another property peculiar to the NMDA receptor is that it must be activated both by glutamate and by membrane depolarization to permit local influxes of calcium ions. This "associative" property enables NMDA receptors in the postsynaptic membrane to potentially discriminate between temporal and spatial patterns of impulses arriving at a given neuron. Evidence that NMDA receptors affect the neuronal morphogenesis of early development primarily comes from experiments with highly selective antagonists of these receptors such as APV [D,L(−)-2-amino-5-phosphonovaleric acid]. But, there have been no clues to indicate which steps in neuronal morphogenesis are affected by NMDA receptor activation and calcium influx.



Dendrite dynamics. The spines on the dendrites of neurons are relatively stable structures. In contrast, the slender extensions of dendrites called filopodia are dynamic, exhibiting both extension and retraction (blue arrows). The red arrowhead indicates the site where a protruding filopodium contacts a neighboring axon, possibly initiating the formation of a synaptic junction. After contact, the filopodium becomes a dendritic spine. The process of filopodial extension and synapse formation is triggered by electrical activity and the activation of NMDA receptors. [Adapted from (*1, 6, 7, 13*)]

Provocative ideas about how electrical activity and neurotransmitter release might affect the morphology of neurons come from dynamic optical microscopy. For example, in living, dissociated neurons in culture the growing tips (growth cones) and filopodia of both axons and dendrites exhibit motility (in the form of membrane protrusions) that can initiate cell-cell contact and synaptogenesis (*6–8*). This form of motility may be modulated by neurotransmitters and

secondary messengers (*9*). Unfortunately, cell culture is a condition far removed from the environment of the neuron in vivo, so the physiological relevance of these findings is still in doubt.

More recently, techniques combining newer fluorescent dyes (such as the lipophilic carbocyanine membrane stains, DiI and DiO) with confocal microscopy have enabled time-lapse observations of single cells within whole embryos and brain tissue slices (*10*–*13*). These studies show that extension and retraction of filopodia occur in tissue slices as well as in cell culture and provide evidence that this motility is modulated by neurotransmitters such as glutamate and electrical activity at synapses. Although these experiments provide access to neurons in appropriate tissue environments, interpretation of the results is restricted by the limits of detection inherent in confocal microscopy and the possible effects of excessive dye and light exposure.

Maletic-Savatic and co-workers have taken advantage of sophisticated new techniques in fluorescence microscopy to observe the dynamics of individual neurons in rat brain hippocampal slices at substantially higher resolutions than achieved before. They used a benign virus that infects neurons to shuttle the gene encoding a soluble green fluorescent protein (GFP) marker into hippocampal neurons. The principal advantage offered by GFP is that it provides excellent fluorescent signals with few toxic side effects (*14*). Finally, these investigators measured fluorescence with a two-photon laser scanning microscope. This new imaging method uses nonlinear fluorescence photoexcitation to achieve optical sectioning and three-dimensional imaging that is far more efficient (in terms of reducing noise and photodamage) than that achieved with the older confocal microscope.

With the improved image quality provided by the combination of these methods, the authors confirm and extend the results of confocal studies (*12*, *13*), including the observation of abundant filopodial protrusions (*13*). They then forged on to investigate the effects of the NMDA receptor blocker APV. Intriguingly, image analysis demonstrated that the firing of action potentials resulted in an increased rate of filopodial formation, which was abrogated by APV. Thus, they demonstrated that the possible morphological target of NMDA receptor activation is the initiation of filopodial extension. This provides an exciting link between NMDA receptor activation and neuronal morphogenesis because filopodial formation has been implicated in synaptogenesis (*7*) (see the figure). In this case, NMDA receptor activation might stimulate the extension of filopodia, which could then contact neighboring axons to initiate cell-cell adhesion and synaptogenesis. Alternatively, NMDA receptor activation might stabilize existing or nascent synapses, preventing their loss. As evidence accumulates that filopodial sprouting is important in synapse formation, it seems that both of these possibilities should be taken seriously. Of course, they are not mutually exclusive. Maletic-Savatic *et al.* note that the very localized control of dendritic filopodial activity by presynaptic action potentials could lead to an associative or "Hebbian" characteristic of synapse formation—that is, axons that fire and release glutamate, thereby triggering local filopodial protrusions, would seem to be more likely targets for synaptogenesis than nonfiring axons at other, more distant sites. These new findings bring to the fore many fascinating questions. What are the mechanisms by which dendritic filopodia protrude, and how are these processes linked to NMDA receptors and calcium influx? Almost certainly, the process involves the actin cytoskeleton (*8*, *15*), but the accessory proteins that generate mechanical force remain to be determined. In addition, filopodial protrusions are obviously accompanied by local rearrangements at the cell surface; these may include exocytotic delivery of membrane vesicles or clustering of molecules specialized for protrusion or adhesion. How do the basic cytomechanical and regulatory schemes for dendritic filopodial formation relate to those governing neuronal filopodial dynamics in other studies of neuronal (*6*, *8*, *13*, *16*) and nonneuronal cells (*17*)? Finally, this work only hints at the part played by filopodial protrusion in synaptogenesis. Much more work is required to establish a definite connection between these two events, and to identify alternative developmental or functional consequences. For instance, the motive forces evident in filopodial protrusion may have their major consequences in more subtle rearrangements of existing synapses rather than in the birth of new synapses (*18*).

References

1. M. Maletic-Savatic, R. Malinow, K. Svoboda, *Science* **283**, 1923 (1999).
2. L. C. Katz and C. J. Shatz, *ibid.* **274**, 1133 (1996).
3. C. H. Bailey and E. R. Kandel, *Annu. Rev. Physiol.* **55**, 397 (1993).
4. M. L. Vallano, *Crit. Rev. Neurobiol.* **12**, 177 (1998).
5. A. B. MacDermott *et al.*, *Nature* **321**, 519 (1986).
6. M. W. Cooper and S. J. Smith, *J. Neurobiol.* **23**, 814 (1992).
7. N. E. Ziv. and S. J. Smith, *Neuron* **17**, 91 (1996).
8. M. Fischer, S. Kaech, D. Knutti, A. Matus, *ibid.* **20**, 847 (1998).
9. S. B. Kater and V. Rehder, *Curr. Opin. Neurobiol.* **5**, 68 (1995).
10. N. A. O'Rourke and S. E. Fraser, *Neuron* **5**, 159 (1990).
11. M. E. Dailey, J. Buchanan, D. E. Bergles, S. J. Smith, *J. Neurosci.* **14**, 1060 (1994).
12. T. Hosokawa, D. A. Rusakov, T. V. Bliss, A. Fine, *ibid.* **15**, 5560 (1995).
13. M. E. Dailey and S. J. Smith, *ibid.* **16**, 2983 (1996).
14. B. Ludin and A. Matus, *Trends Cell Biol.* **8**, 72 (1998).
15. A. Matus, M. Ackermann, G. Pehling, H. R. Byers, K. Fujiwara, *Proc. Natl. Acad. Sci. U.S.A.* **79**, 7590 (1982).
16. S. J. Smith and C. E. Jahr, in *The Nerve Growth Cone*, P. C. Letourneau, S. B. Kater, E. R. Macagno, Eds. (Raven, New York, 1991), pp. 19–26.
17. H. Miki, T. Sasaki, Y. Takai, T. Takenawa, *Nature* **391**, 93 (1998).
18. F. Crick, *Trends Neurosci.* **5**, 44 (1982).

PERSPECTIVES: ORIGIN OF EARTH AND MOON

Colliding Theories

Alex N. Halliday and Michael J. Drake

How did Earth and the moon form? And what forces defined their basic physical structures? These key issues in Earth and planetary sciences have for many years been at the borderline of tractability. Advances have come mainly with progress in simulating the dynamics of planetary accretion, in measuring isotopes that act as chronometers for early solar system processes, in analysis of noble gas isotopes that yield clues about the early atmosphere, and in melting experiments at previously unattainable pressures and temperatures. A recent conference in Monterey, California (*1*), showed that, although a general picture may be emerging, many issues remain hotly debated.

Planet formation is thought to start with sticking and frictional coagulation of dust particles in a gaseous nebula that persisted in the circumstellar disk. The particles grow in size until there is substantial gravitational attraction between kilometer-sized bodies, which coalesce further. Major collisions between small proto-planets eventually result in objects the size of Earth. The energy of late-stage planet-building impacts would be colossal, sufficient to melt the entire planet. Magma oceans would be formed, and some volatile elements would escape into space.

The most widely accepted theory for the origin of the moon is that it coalesced from a ring of debris produced by such a

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