Intrinsic activity in cells and the brain

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ABSTRACT **Motile cells such as bacteria, amoebae, and fibroblasts display a continual level of energy-consuming reactions involving the cytoskeleton and signal pathways, regardless of whether or not they are actually migrating. I draw parallels between these "silent signals" and the intrinsic activity of the human brain, especially that associated with the brain stem. In both cases, it can be argued that the organism continually rehearses possible future actions, so it can act quickly and accurately when suitable cues are received from the environment.**

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The behavior of higher animals such as mice and monkeys seems to have little in common with that of bacteria and amoebae. Not only are the organisms a millionfold different in size, but they also move in totally different ways. In one case a vast, complex network of electrically active cells controls an orchestra of powerful contractile machines. In the other, a water-based slurry of proteins and other molecules creates movement through self-association and chemical reactions. And yet—perhaps because of their common ancestry and shared need to survive in the same unpredictable environment—the two kinds of organisms may indeed exhibit similar strategies. Both have to work within an energy budget. Both must prioritize certain crucial actions, so they are as fast or powerful as possible. Moreover, any motile organism, regardless of size, can gain a huge advantage over its prey or competitors if it can anticipate future events, even by a tiny margin. Perhaps for this reason, we find that both higher mammals and single cells (and by implication everything in between) generate movements in a "proactive" mode. That is, they do not move, as often assumed, solely in response to the momentary demands of the environment. Rather, their actions are selected from an upwelling of spontaneous activity that serves to anticipate incoming stimuli.

The most direct evidence for a high level of intrinsic activity in the brain comes from positron emission tomography, an imaging technique used to measure blood flow. The related technique of functional magnetic resonance imaging allows the high levels of spontaneous activity to be visualized. These methods are typically used to pinpoint local changes due to the performance of a particular task. However, if the raw data are examined without the usual background subtraction, then the entire brain is seen to seethe with activity in an unceasing stochastic display (Raichle, 2010). The patterns change only marginally if the subject performs a particular task, no matter how vigorous or intellectually challenging (Sadaghiani and Kleinschmidt, 2013). Indeed, some tasks result in a local decrease rather than increase of activity.

Evidence for intrinsic activity also comes from measurements of energy consumption. The human brain consumes something like 20% of the total body energy while accounting for only 2% of body weight. As with activity patterns, however, the level of energy consumption by the brain is little affected by task performance.

If we ask more specifically *where* the movements of higher animals come from, then we have to look to the brain stem. There, an unstoppable font of electrical activity creates a plethora of meaningful signals that reverberate between basal ganglia and the thalamus. Most signals fail to reach the cortex or activate muscle contraction, because they are inhibited. Only when a suitable stimulus is received from the environment will selected pathways be released from their inhibition to complete their circuit and fire a motor response (Llinás, 2002). The advantage of this seemingly wasteful approach is believed to be that the animal can continually rehearse and refine potential moves ("fixed action patterns") in a silent manner. When the time comes, release is swift and accurate (Smith, 2012).

Moving to the other extreme, we know that the actions of single free-living cells such as bacteria and protozoa are often rapid and highly specific. They can be guided by external cues such as chemical flavors, light, sound, and physical forces. We also know that single-cell behavior entails complicated cascades of biochemical changes, typically starting at sensory receptors in the membrane and diffusing into the cytoplasm, where they activate cytoskeletal structures responsible for movements. But are these reaction pathways made to order on receipt of the environmental stimulus? Or could it be that, as in the brain, parts of the circuit are continually rehearsed in anticipation of the incoming stimulus? Recall that fast, accurate reflexes are just as important for the survival of these tiny creatures as for a fox or rabbit. The tyranny of natural selection still applies.

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Several observations suggest there could be something in the idea. To begin with, it seems that any cell with the potential to crawl or swim maintains a high level of internal activity. An *Escherichia coli* bacterium, for example, is always swimming, regardless of whether it is tracking down food, avoiding toxic substances, or simply suspended in an ionic solution (Berg, 2004). Flagellar motors turn continuously, and external influences act solely by modifying their direction of rotation: in the absence of food, the bacterium hunts incessantly, testing first this direction then another. Quantitative analysis of this intrinsic "noise" supports the view that it primes the organism for future action; the more noisy the prestimulus behavior, the larger the eventual response (Park *et al.*, 2010).

In a recent analysis of the biochemical reactions underlying the chemotactic response of *Dictyostelium* amoebae—a world apart from bacteria in molecular terms—two patterns of intrinsic activity were found (Huang *et al.*, 2013). The first was an oscillation in the actin-based cytoskeleton that was largely autonomous and independent of external influences. The second was a more sporadic firing of a control circuit involving kinases and GTPases that was considered sensitive to multiple factors. These two activities apparently work together such that the migration of the cell can be guided by external factors, chemical or electrical.

Even cells in a mammalian organism continually recycle their cytoskeleton. A nerve growth cone labeled with fluorescent actin, for example, displays an unending roiling motion as new filopodia and other protrusions form at the leading margin, while others are pulled back into the cell (Betz *et al.*, 2009). In epithelial cells, actin filaments show continual polymerization and depolymerization at the leading margin as revealed by speckle fluorescence (Ponti *et al.*, 2005). Significantly, these movements continue unabated whether or not the cell itself is moving forward, like an automobile engine in neutral gear. They take effect only sporadically through the action of a postulated molecular clutch (Welf *et al.*, 2013).

All of the above cellular movements burn ATP. In a swimming *E. coli*, a cascade of reactions involving a protein kinase and two downstream proteins hydrolyzes ATP in order to maintain critical components at a suitable level of phosphorylation. Numbers of phosphorylated target proteins fluctuate rapidly as phosphate groups are added and removed, thereby controlling the direction taken by the cell. Similarly, the dynamic turnover of actin filaments in a fibroblast is driven by the consumption of energy. As filaments grow, monomers add to their free ends, and the ATP they carry is hydrolyzed; as filaments shrink, their monomers are released to the cytosol to pick up fresh ATP. Remarkably, the turnover of actin filaments represents as much as 50% of the total ATP utilization of resting platelets (Daniel *et al.*, 1986), and a similar figure has been obtained for cultured chick neurons (Bernstein and Bamburg, 2003). Energy consumption in the "resting state" evidently far exceeds that produced by any specific stimulus. Once again, as for brain activity, the extra energy consumption required to perform any specific movement is marginal.

Much of the basal activity of a cell is related to cyclical reactions. A significant proportion of enzymes of intermediary metabolism and most if not all signaling proteins shuttle between two states. Sometimes the protein is chemically modified through the addition and loss of a covalently bound group, such as phosphate or acetate (as in *E. coli* chemotaxis). Elsewhere, the protein changes its conformation through association with another protein or a small molecule such as a nucleotide phosphate (the basis of the dynamic assembly of actin filaments and microtubules). More complex cycles are seen at the level of gene expression, in which key transcription and regulatory factors are found to pulse on and off repeatedly, and often stochastically, even when cells are maintained in constant conditions (Levine *et al.*, 2013). This type of spontaneous dynamic behavior is pervasive, appearing in diverse cell types from microbes to mammalian cells.

Cyclic reactions were originally termed "futile" because they appeared to burn energy to no purpose. They are now recognized as essential for the dynamic properties of cells. For one thing, they enable cells to respond quickly, because changes in molecular concentration can occur at the speed of the cycle. More importantly, they also provide an endless source of noisy, exploratory behavior in which the cell is able to "rehearse" possible future actions.

The actions available to an organism are limited by its energy budget, and food is often in short supply. So it seems paradoxical that creatures large and small should invest a major proportion of their energy simply in order to, so to speak, "tread water" or "jog in place." What sense does this make from an evolutionary standpoint? Perhaps—as suggested in the case of the brain—intrinsic activity allows the organism to prepare for a range of possible actions. Even in microorganisms, circuits could maintain patterns of activity (analogous to the fixed action patterns of the brain stem) appropriate to well-defined coordinated movements, such as eating, exploring, mating, or escaping. These circuits could be created by experience, heredity, or both, but then maintained in a "silent" or "primed" condition in which they generate no actual movement. This incipient activity would serve, in effect, as an internal representation of the external world, continually updated, that anticipates the most likely actions to be required next. If and when an incoming sensory stream fulfills one of these predictions (as it usually does) then the system will fire and a fully formed motor action be produced with minimal delay.

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