Darwin's motors

George Oster

In 1827, Robert Brown famously observed under his microscope pollen grains dancing as if alive. At first he thought he might be observing the "elementary molecules of organic bodies" — the life force itself. And, in a sense, he was. The pollen grains were not 'alive', but were being driven by the thermal motions of the surrounding fluid molecules.

A complete explanation of Brown's observations came with Einstein's 1905 theory of 'brownian motion' and its experimental confirmation by Jean Baptiste Perrin, who won the 1926 Nobel Prize for his work (Einstein's theory did not — what were they thinking?).

Brown was right about the movements he observed being the 'life force' because the chemical reactions on which life depends are driven by brownian motion. Enzymes must explore millions of configurations per second to seize on the correct one that allows a reaction to take place. Thermal fluctuations at the molecular scale are almost unimaginably tumultuous, and are easily up to the task.

Motor enzymes use energy stored in chemical bonds to generate directed forces for an amazing variety of tasks. Despite their variety, they all operate on the same principle: they trap brownian fluctuations, albeit in different ways. One mechanism involves biasing, or rectifying, the otherwise random brownian movements by using short-range attractive forces to trap favourable fluctuations. For example, a polymer can push a load ahead of it as it polymerizes. Here the brownian motion of the load (and of the polymer itself if it is flexible) eventually opens up a gap large enough for a monomer to insert itself between the load and the polymer tip. Thus the load is prevented from diffusing backwards once the monomer is in place — it is driven forwards in monomer-sized steps, using the energy that binds the monomers together to ratchet the fluctuations of the filament and the load.

This 'brownian ratchet' mechanism is how many intracellular parasites propel themselves through their host's cytoplasm. A similar process moves unfolded proteins through the membranes of cell organelles: 'trapping' proteins bind to the portion of the target protein diffusing through a transmembrane pore, preventing it from going backwards again.

The speed of this kind of ratchet varies inversely with the size of the load, so large loads tend to move slowly. Moreover, the motor can be used only once, and is then disassembled into its subunits and reassembled anew. But a protein's catalytic site is flexible so that it can respond to smaller, and therefore much more frequent, brownian fluctuations, rather than waiting for the load to diffuse over a large distance. These smaller ratchet steps enable motor proteins to form direct, elastic couplings with their load and to drive it with a power stroke using the energy acquired by binding to a substrate protein.

This binding is progressive: the protein wraps around its substrate, each step driven by ångström-sized brownian fluctuations that bring the protein and substrate atoms within range of intermolecular attractions that trap the fluctuation. (The wrapping of the catalytic site around the substrate is stochastic, so fluctuations in the opposite direction can unwrap as well, but the intermolecular attractions favour wrapping.) As the intermolecular bonds between enzyme and substrate 'zip up', they induce a strain in the binding site that is used to lever the load over distances that are comparable to the size of the protein itself. The biochemist Daniel Koshland first proposed the idea of an 'induced fit' between an enzyme and its substrate, although he was not thinking specifically about motor proteins.

Enzymes that use this 'small fluctuation' mechanism have the further advantage that they can operate in a continuous cycle by using a 'fuel' molecule — usually ATP in cells — as a binding partner. After binding to the motor and driving the power stroke, this nucleotide can be cleaved into two. Each piece can then be knocked out of the binding site by brownian fluctuations, freeing the site to bind to another ATP molecule. Thus brownian motion drives both the power and exhaust strokes.

Many motor enzymes combine both of these mechanisms to generate a directed force. Some resemble two 'legs' that step along a polymer track between equally spaced binding sites. The 'front' leg of the enzyme is driven forwards, and then 'hunts' by diffusion for the next binding site along the track. When the front leg is close enough to the next site, the excursion is trapped and a ratcheting of brownian motion has taken place. These 'walking motors' use two binding partners: attachment to the track sites generates a power stroke, whereas cycling of ATP provides the energy to break free for another step. The physiologist Andrew Huxley first proposed a mechanism of this sort for myosin, the motor protein that drives muscle contraction.

One of the most remarkable motor enzymes is F_1F_o ATPase, possibly life's most abundant protein, which catalyses the production of ATP. (Every day, we produce — and consume — about half our body weight in ATP!) This enzyme consists of two rotary motors attached to a common shaft. The F_1 motor generates a power stroke using ATP as its fuel; the F_o motor is almost a pure brownian ratchet that uses the binding and release of protons flowing through it to rectify its rotational diffusion. More than any other, this protein has illuminated our knowledge of the miniature motors that form the true basis of Brown's 'molecules of life'.

In a broader sense, the idea of generating order by 'selecting' from random variations is hardly new — it is the fundamental idea of Darwin's theory of natural selection. In the context of motor proteins, the 'order' created is a directional force, and the agents of selection are intermolecular attractions. Hence the idea of a brownian ratchet keeps popping up in new contexts, providing a fertile stimulus to our thinking in disparate fields. Indeed, as the philosopher Daniel Dennett has said — and I agree — Darwin may have had the best idea that anyone ever had. Think about it. ■

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Molecular ratchets mirror mechanical ones.

Brownian ratchets

The molecular motors on which life depends are driven by brownian motion.

FURTHER READING

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