NEUROBIOLOGY

Hit and miss

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No matter how hard you practise a movement, you can never be entirely sure how it will turn out. Shouldn't the same action executed under the same conditions always produce the same result? Yet even professional darts players, throwing in a controlled indoor environment and standing a set distance from the board, can miss the bull's-eye.

Many theories of muscle control have assumed that such errors arise from variation generated during the movement — particularly 'noise' in the way that neurons pass instructions to the muscles at the neuromuscular junction. But Mark Churchland, Afsheen Afshar and Krishna Shenoy report that a large part of the problem could instead arise as the brain plans the action (*Neuron* **52,** 1085–1096; 2006).

They observed monkeys reaching for visual targets that appeared on a screen. When a target first appeared, it jittered slightly in place, and the animals were trained not to reach for it until it became stationary a half-second to a second later — allowing a period of preparation.

The authors recorded neural activity from the motor cortex and the premotor cortex, two brain regions involved in movement planning and execution. Comparing the monkeys' reaching movements with these recordings, they found that variations in the velocity of the reaches correlated with fluctuations in brain activity during the preparatory period — hundreds of milliseconds before the movement started.

So it seems that the execution of even a simple, well-practised task is limited by the brain's ability to plan the same movement over and over again. Indeed, Churchland and colleagues estimate that this constraint could account for at least half of the variability in the monkeys' movements.

Whether the fluctuations they observe actually arise in the premotor and motor cortex, or merely reflect variations elsewhere in the brain, is still an open question. And how variations in sensory input might affect the subsequent movement has yet to be fully explored. Finding the answers will have implications for our understanding of how the brain controls movement, and in the long term could have an impact on how movement disorders are treated.

Helen Dell

Surprisingly, Acquisti and colleagues' analyses suggest that the main distinctive feature of these novel transmembrane proteins is that they are enriched in oxygen atoms: in particular, their oxygen-rich external domains are longer than those of transmembrane proteins from uncompartmentalized cells.

How might levels of atmospheric oxygen have constrained the atomic composition of transmembrane proteins? Acquisti *et al.* propose two hypotheses. The first, inspired by stoichiometric ecology[7], is that, in the absence of O_2, building oxygen-rich amino acids would have been too demanding. However, there is no obvious evidence for such a metabolic limitation. According to computational analyses[5], the seven amino acids containing most oxygen atoms — D, E, Y, S, T, N and Q, in single-letter code — could all be synthesized by anoxic metabolisms. Moreover, among the 86 final reactions producing these amino acids, only 11 are specific to the oxic metabolism[5,8]. The authors thus favour the second hypothesis: that the reducing atmosphere found under low levels of O_2 would have damaged long, oxygen-rich protein domains, and made the synthesis of transmembrane proteins with long external parts impractical.

The work of Acquisti *et al.*[1] could be refined by correlating the oxygen content of transmembrane proteins with that of the compartments in which they are embedded. In particular, intracellular membranes delineating reducing compartments would be expected to contain more oxygen-poor proteins than does the plasma membrane. A candidate for such a study would be the membrane of mitochondria, the cell's energy-producing compartments. As a result of their continuous consumption of oxygen by respiration, mitochondria are the most anoxic compartments of oxygen-respiring cells.

Moreover, a striking difference between most eukaryotes and most prokaryotes is that respiration does not occur in the eukaryotic plasma membrane. As a consequence, O_2 is not consumed in the immediate proximity of eukaryotic plasma membranes, which thus exist in an oxygen-rich environment. Seen in the light of Acquisti and colleagues' paper, this may have been a factor in protecting their oxygen-rich transmembrane proteins. The O_2-driven emergence of multicellular organisms may therefore have required two major changes: accumulation of oxygen-rich proteins in the plasma membrane and confinement of respiration to intracellular compartments dedicated to that purpose.

It is striking that it has taken so long to make these simple observations on the elemental compositions of transmembrane proteins, and to formulate the resulting model of evolution[1]. The main reason may be that biologists usually regard proteins as chains of amino acids, or combinations of polypeptide domains, and ignore the fact that, in essence, proteins are arrangements of atoms. The elemental structure of biopolymers may well have been shaped by nutritional, physical or functional constraints[9], but the effects of these constraints usually remain hidden if one inspects only the amino-acid (or base-pair) compositions.

The work of Acquisti *et al.* is a welcome reminder that such constraints acted on subsets of proteins linked by function[10], cellular location[1] or metabolic role[11], as well as on the total protein content of a cell[12]. Structural biologists are no longer alone in keeping the atomic composition of their favourite proteins under close scrutiny — evolutionary biologists, too, will find this a fruitful pursuit. ■

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