ceutical industry can be expected. There is little doubt that organocatalysis is here to stay.

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STRUCTURAL BIOLOGY

Dynamic Visions of Enzymatic Reactions

Experimental evidence is provoking further discussion of a stochastic view of protein behavior.

Michele Vendruscolo and Christopher M. Dobson

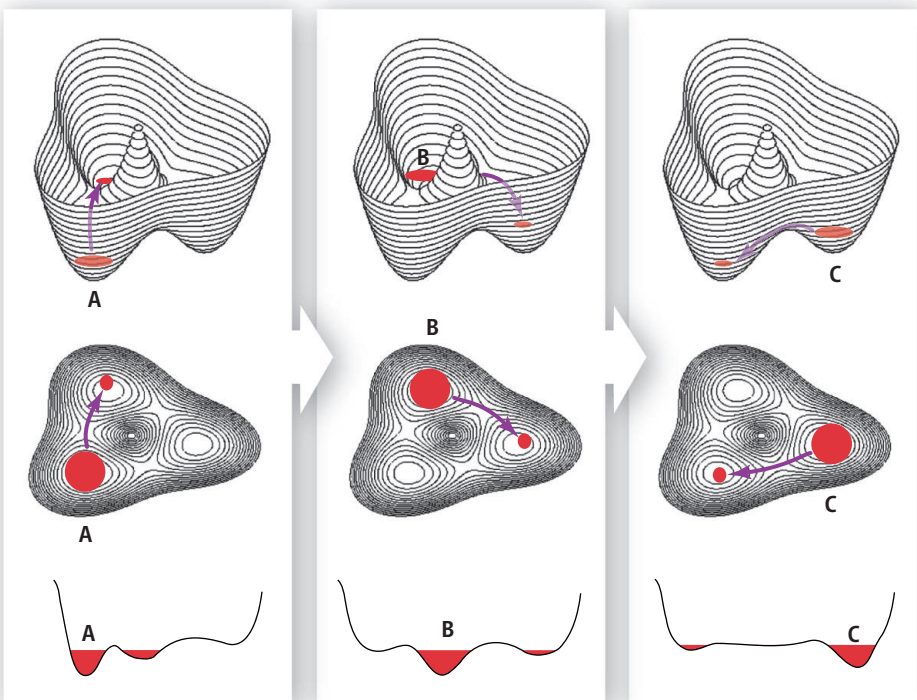
The action of many proteins involves large-scale conformational changes that typically take place on the millisecond time scale. Examples include the cooperative transitions that enable efficient oxygen transport by hemoglobin in the blood, and the series of motions involved in muscle contraction (*1*). But even proteins that do not undergo such dramatic conformational excursions are not the rigid objects that structural models often imply. The conformations of all proteins constantly fluctuate, with some motions taking place on time scales of a picosecond or less and involving displacements in atomic positions of ~0.1 nm (*1–6*) .

Are these motions simply inherent properties of molecules held together by relatively weak interactions, or have they evolved to enhance their functional efficiency? There is increasing evidence that both views may in fact have validity and that biology has channeled the inherent motions of proteins into directions that enhance their effectiveness. For example, structural fluctuations of enzymes appear to increase the probability of binding certain ligands, although more studies are needed to establish their effects on the catalytic rates themselves. On page 1638 of this issue, Boehr *et al*. (*7*) report experimental evidence that is interpreted in terms of this view of enzymology. They also indicate that many fluctuations can be linked together into whole reaction cycles that carry out a complex chemical process with great efficacy.

In recent years, the idea that random conformational fluctuations of proteins are channeled into productive events has gained popularity. This concept is rooted in a statistical view that has revolutionized, for example, our understanding of protein folding (*1*, *2*, *8–10*), a process now perceived not as a deterministic sequence of well-defined conformations, but rather in terms of stochastic events along free-energy landscapes that funnel the molecular fluctuations toward their native structures. The "jigglings and wigglings" of protein molecules anticipated by Feynman (*11*) appear therefore to have been harnessed for specific purposes during molecular evolution.

Application of this statistical view to enzyme behavior suggests that conformational fluctuations resulting from the concerted motions of many atoms can push the unbound states of enzymes into conformations closely resembling the bound states, thereby priming them to form complexes with specific ligands (*5*, *12*, *13*). Thus, although the unbound state of a protein is inherently flexible, fluctuations are not random. Rather, they take place preferentially in a way that prepares the protein to bind to its cofactors and substrates. The free-energy landscapes of the free and the bound states differ just enough to cause changes in the relative populations of their principal states. After binding, the free-energy landscape (*7*) is plastically deformed just enough to make a slightly different state of the protein become the most populated (see the figure).

Boehr *et al*. suggest that certain enzymes can combine flexibility with plasticity to



A free-energy channel model for enzymatic behavior. The binding of a ligand shifts the predominant population of enzyme molecules from the free state (**A**) to a bound state (**B**) that was previously sampled transiently through stochastic fluctuations. Further conformational fluctuations from **B** enable the catalytic state (**C**) to be accessed. When the enzyme returns to state **A**, the cycle can begin again.

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achieve a sophisticated series of changes in structure and dynamics. According to this view, for each state along the enzymatic cycle of dihydrofolate reductase (DHFR) (*14*), a binding event can cause a protein molecule to occupy a new free-energy minimum (see the figure), stabilized by a ligand and geared to fluctuate toward another state that binds the next ligand in the catalytic cycle. The five successive steps of such transitions that exist in DHFR would thus show just how effectively evolution can coordinate the thermal motion of hundreds of atoms to perform biological functions.

If this view turns out to be correct, then the free-energy landscapes of enzymes would not just be funnels; rather, they would appear more as a set of coupled low-energy states. In the case of catalytic cycles, these free-energy landscapes could be merged into rings that resemble perhaps rather battered sombreros (see the figure). Such a shape can be created by stringing together several free-energy funnels, one for each of the structurally quite similar states along the catalytic cycle. The alignment of these funnels could result in a channeling mechanism that generates the complex motions required for enzymatic activity by breaking them down into simpler ones that are closely coupled to each other.

Although much remains to be learned, this free-energy channel model may be the result of a general type of free-energy surface characterized by statistical pathways that enable the performance and regulation of catalytic reactions by a succession of binding events. Increasingly complex reactions could be realized by generating further funnels along the channel. Exploration of these concepts will be particularly relevant in view of the increasing realization that enzymes—and other proteins—act as part of complex networks of interconnected processes.

Boehr *et al.* infer the structural similarity of an excited state with the ground state of the following step of the enzymatic cycle from the correlations between the chemical shifts of these states. Recent advances in protein structure determination (*5, 15*) using the same sort of nuclear magnetic resonance data that can be extracted from the type of experiments carried out by Boehr *et al*., suggest that detailed structures of the excited states themselves could be just around the corner. Examination of such structures would undoubtedly enable these interesting concepts to be tested further and could also shed light on the role of the multiple protein-protein interactions now being discovered through proteomic techniques, and be of great practical value for rational drug design.

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PHYSICS

Detecting and Controlling Electron Correlations

Measurement and control of fluctuations in circuits may lead to devices for quantum computation.

Markus Büttiker

As electronic devices shrink to nanometer dimensions, their properties are increasingly governed by quantum effects rather than by classical physics. Electron motion is no longer a simple matter of electrical currents flowing in circuits, but is instead highly influenced by the diffraction and interference of the particle wave functions as described by quantum mechanics. In this case, the fluctuations exhibited by electron currents may contain information that is fundamental to understanding physics at nanometer scales. The ways in which such fluctuations are correlated in a nanostructure are interesting, especially for the possible construction of quantum information-processing elements. A recent experiment by Oberholzer *et al*. (*1*) shows how the quantum correlations between current fluctuations at two contacts of a normal conductor can be controlled simply by tuning an electrode voltage.

The physics of current fluctuations has been the subject of much experimental and theoretical exploration. The findings of Oberholzer *et al.* in particular confirm a theoretical prediction about current correlations made by Texier and Büttiker in 2000 (*2*). Previously, the sign of the current-current correlation measured between contacts in a device has always been connected to the statistical properties of the carriers (*3*). Electrons are fermions and the Pauli principle dictates that each state can only be singly occupied; as a consequence, current-current correlations in normal conductors are negative. Conversely, for current carriers that obey Bose-Einstein statistics (in which a given state can be occupied by multiple quanta), positive correlations are observed. To reverse the sign of these correlations, the experiment brings another effect into play: Electrons are carriers with charge. A charge imbalance leads to an electric field that in turn acts on all electrons in the same way within its range, leading to additional correlations. These correlations can dominate the antibunching effect of the Pauli principle and lead to positive correlations even in a purely normal conductor.

The geometry analyzed theoretically (*2*) and used in the experiment (*1*) is shown in the figure. The conductor consists of a high-mobility two-dimensional electron gas with a geometry determined by top gates (A, B, C in the figure). If a voltage is applied to the gates, they deplete the electron gas underneath them, thus generating the desired geometry. The conductor consists of two narrow orifices called quantum point contacts (QPCs), labeled A and B. Electron current is incident at contact 1, and the current

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