

When we think of enzymes, it's common to imagine them as keys that fit into locks: molecules that receive reactants in the right place and make the chemistry of life happen with precision and speed. This image is still true, but incomplete. Within these structures, something more subtle also occurs: electrons move like invisible travelers, traversing the interior of the protein in paths that resemble tunnels, bridges, or small energy islands. At some points, they jump between aromatic rings; at others, they follow rows of metal atoms that function as conductive tracks. Seen from this perspective, the enzyme ceases to be merely a chemical machine and becomes an electronic landscape, with insulating regions, high-conductance pathways, and zones sensitive to pH, water, and the molecule's momentary shape. It's as if each protein were a living circuit, shaped not by wires and semiconductors, but by atoms, charges, and evolutionary history. Seen through the electron's eyes, the interior of an enzyme is a rugged terrain. There are chemical bridges that facilitate communication between one point and another, nonpolar regions that hinder progress, and pockets of water and ions that change the landscape in fractions of a second. Physicist Rudolph Marcus showed that the speed at which an electron makes the jump depends on two factors: the quality of the bridge and the flexibility of the surrounding environment. If the path is well-connected and the environment requires little adjustment, the electron crosses quickly. But if the bonds are weak and the environment vibrates excessively, the jump is slow or requires longer detours. Over short distances, the electron can cross directly, as if traveling through a narrow tunnel; over longer distances, it jumps from step to step, using amino acids or chemical cofactors as footholds. In reality, proteins combine these two modes of travel, and the electron chooses its route based on the "energy profile." There's another factor guiding this electronic map: the evolutionary history of proteins. When comparing enzymes from different species, amino acid sequences that change in a coordinated manner are like finely tuned knobs over time. Many of these points aren't at the center of the reaction, but rather nearby, where they influence the local electric field, substrate access, and the stability of chemical intermediates, or far away, where they establish fields directing large-scale functional movements. Small amino acid changes can alter the entire scenario: changing a residue here or there can alter the path through which electrons and protons flow. This happens because mutations rarely act alone; one depends on the other, in a game of trade-offs called epistasis. It is through this subtle choreography that evolution adjusts, refines, adapts to environmental changes, and sometimes completely transforms an enzyme's electronic pathway. Some proteins have taken this art of conducting electrons to the extreme. So-called multi-heme metalloproteins are a striking example: in them, heme groups—small structures with an iron atom at the center—line up like beads on a necklace. Each heme can accept and donate electrons, and together they create an efficient corridor for charge transport. In certain bacteria that thrive on electricity, such as *Shewanella oneidensis*, this arrangement forms veritable biological wires that traverse the cell membrane, a natural insulator, conducting electrons over distances of several nanometers. Interestingly, this conduction is virtually temperature-independent, indicating a strong connection between the cofactors. Recent studies even suggest that these pathways can distinguish electrons by their spin, a kind of quantum "polarization," as if the proteins had a built-in magnetic sensitivity. When scientists compare the sequences of these enzymes, they realize that small differences in the amino acids surrounding the heme groups can strengthen or disrupt these pathways, revealing where nature has refined, through trial and error, the circuits of life. Not all electron pathways serve solely to transport energy or information; some exist to protect the enzyme itself. Certain amino acids, such as tyrosine and tryptophan, function as "safety rails" within the protein. When the active site is exposed to strong oxidants or light, these molecules assume the role of emergency conductors: they guide the positive charge, or the "hole" left by a lost electron, to safer regions, where reducing agents can neutralize it. This process, known as hole hopping, prevents damage to the catalytic center without interrupting the reaction. One of the most impressive cases occurs in ribonucleotide reductase, an enzyme that depends on a precise sequence of electron and proton jumps to function. The transport of positive charge can span tens of angstroms, in a ballet of coordinated events that keeps the reaction under control. Interestingly, when researchers compare variants of this enzyme in different organisms, they find subtle changes in the positions of tyrosines and tryptophans, as if evolution had carefully redrawn the paths these holes travel. Beyond the physical pathways, there is also the energy relief map within enzymes, an invisible portrait of energetic mountains and valleys, where it is difficult or easy for an electron to pass. In many ways, this map resembles that of an amorphous semiconductor, with regions where electrons can flow freely. In proteins, this relief is molded by charged amino acids, such as lysine and arginine (positive) or aspartic and glutamic acid (negative), as well as the protonation state of histidine and the presence of water and ions nearby. These elements push and pull energy levels, creating

intermediate steps that serve as supports for electronic leaps. Cofactors such as heme groups and flavins add new “floors” to the energy edifice, adjustable by factors such as pH, ionic strength, and even the binding of a metal atom. Decades of electrochemical studies and simulations have shown that proteins act, in a sense, like programmable materials—systems capable of shaping their own electronic states to optimize vital chemical reactions. Enzymes also adjust their energy levels with a precision reminiscent of an engineer. Small changes in the cofactor’s environment—swapping an atom that binds to the metal, altering the degree of hydrophobicity, or moving a charge—can shift the redox potential by hundreds of millivolts. It’s like tuning an instrument: just a small adjustment is enough to completely change the tone of the reaction. Experiments with proteins like cytochrome c and microperoxidase show that the environment surrounding a heme can make electron transfer easier or more difficult, depending on how the hydrogen bond network is organized. Even in proteins created from scratch, researchers can manipulate the “internal electric field” to control the flow of charge. Nature has been doing this for billions of years, and understanding how it does it can teach us how to design more efficient catalysts and biological circuits that respond to the slightest signal. The shape of the pathway is as important as the energy that moves the charge along it. Between the starting point and the destination, the protein offers a veritable quilt of chemical bonds, hydrogen bonds, and uncharged pockets. The electron moves more easily through firm bridges than through empty spaces, and the molecule’s natural vibrations can both open and close these passages. When viewed as a wave, the electron also has the potential to pass through small empty spaces or tunnel through energy barriers. When the cofactors are close and well-aligned, transport can occur almost coherently, as if the electron were gliding in a single motion. But as distances increase and the medium becomes more flexible, it must proceed in stages, triggered by heat and fluctuations in the environment. These differences, known to physicists in organic semiconductor materials, are now also observed in individual proteins. In remarkable experiments, scientists have anchored enzymes between tiny electrodes, measuring how electrical current passes through them. These studies, using techniques such as scanning tunneling microscopy and single-molecule junctions, are revealing that even living matter can conduct electricity with an elegance that no copper wire could imitate. These discoveries aren’t just beautiful theories; they inspire concrete experiments. If certain charges within an enzyme function as dopants in an electronic material, then swapping a charged amino acid for a neutral one can change how the protein conducts electricity. Changing a lysine residue to glutamine, for example, can shift energy levels and modify the current curve observed in an experiment. Similarly, if tyrosines and tryptophans serve as rails for draining positive charges, deactivating them by mutation increases oxidative damage and shortens the lifetime of radicals observed by electron paramagnetic resonance. pH and ionic strength also come into play, reshaping the protein’s internal energy map and altering the height of the barriers an electron must overcome. These ideas are tested with instruments that seem straight out of science fiction: electrochemical scanning tunneling microscopes, conductive force probes, and single-molecule junctions, capable of measuring electron flow through a single enzyme. Each mutation, each change of environment, offers a new clue about how to transform the chemistry of life into living engineering. All of this leads us to a simple but profound question: what kind of electronic material is an enzyme? The answer depends on the context. Under normal physiological conditions, a hydrated globular protein tends to behave like an insulator, its electrons trapped in local orbits, without suitable bridges to cross. But simply introducing metallic cofactors, adjusting the pH, or rearranging charges can cause it to act like a molecular semiconductor, where electrons advance in small leaps through aromatic amino acids and metal atoms. In some exceptional cases, such as in the chains of aligned heme groups in electroactive bacteria, true high-conductance wires emerge, in which the electrical flow is almost independent of temperature. These proteins are rare but valuable: they demonstrate that the boundary between biology and electronics is not a barrier, but a continuum. Nature, it seems, learned to build circuits long before us. The emerging insight is astonishing. Enzymes are not only reaction catalysts, but also living electronic materials, capable of acting as insulators, semiconductors, or even good conductors, depending on the environment and molecular architecture. In this sense, other protein structures and other macromolecules that make up living beings can be considered as containing electronic structures and circuits responsible for molecular recognition and signaling. This flexibility creates a bridge between biochemistry and solid-state physics, demonstrating that the principles governing silicon also manifest organically in living matter. Understanding these connections could usher in a new era of design: catalysts that respond to electrical signals, more sensitive biosensors, and biocircuits that communicate directly with electronic devices. The 20th century miniaturized silicon circuits; the 21st century may teach us how to cultivate them in proteins. Instead of rigid doping and perfect crystals, we will have states shaped by biology, electronic

bands born from the movement of molecules and electrons traveling through the vibrant rhythm of life.