viruses is preadapted, the disease will be more severe.

Differences between populations, similar to those for class I MHC, occur for class II and for immunoglobulin allotypes; these too, influence pathogens' virulence. Limited DNA diversity in Amerinds was emphasized by Sullivan's use of the Kidds' data from a South American tribe to show that DNA fingerprinting methods do not always distinguish between persons (*12*). Pathogen adaptation to populations with limited diversity may involve many agents other than RNA viruses. More complex parasites carry multiple interchangeable genes that function like hypermutability in avoiding immune responses and take about the same amount of time to switch (*13*). With reduced polymorphism at many loci and exposure to diverse mutable pathogens, it is not surprising that previously isolated people fared poorly. Intermarriage between populations reduces the problem, but an unfortunate consequence of intermarriage is often the loss of indigenous culture.

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Electron-Tunneling Pathways in Proteins

David N. Beratan, José Nelson Onuchic, Jay R. Winkler, Harry B. Gray

Electron-transfer (ET) reactions are key steps in photosynthesis, respiration, drug metabolism, and many other biochemical processes. These ET processes commonly occur between protein-bound prosthetic groups that are separated by large molecular distances (often greater than 10 Å). Although the electron donors and acceptors in these reactions are expected to be weakly coupled, the ETs are remarkably fast and proceed with high specificity. On page 1748 of this issue, Pelletier and Kraut (*1*) present work on the crystal structures of cytochrome c–cytochrome c peroxidase complexes that could lead to a much deeper understanding of how the intervening medium controls interprotein ET reactions.

Theoreticians have been intensely interested in long-range protein ET reactions for many years. In standard formulations, the weak electronic coupling between distant donor and acceptor sites leads to rates that are proportional to a protein-mediated electronic-coupling factor, $|T_{DA}|^2$, and a nuclear factor that arises from nuclear motion coupled to the ET process (*2*). The simplest models describing long-range protein ET treat the medium between donor and acceptor as a one-dimensional square tunneling barrier (1DSB); accordingly, the rate (k_{ET}) is predicted to drop exponentially with distance (*3*, *4*). Accounting for the role of protein-mediated coupling in the 1DSB models amounts to assigning a barrier height for electron tunneling. Estimates of the exponential decay constants (β) made in the 1970s by Hopfield (1.4 Å^{-1}) (*3*) and Jortner (2.6 Å^{-1}) (*4*) stimulated numerous experiments on small molecules and proteins.

A simple formulation of the electronic-coupling problem in long-range ET describes the medium between donor and acceptor as a bridge comprised of identical repeat units:

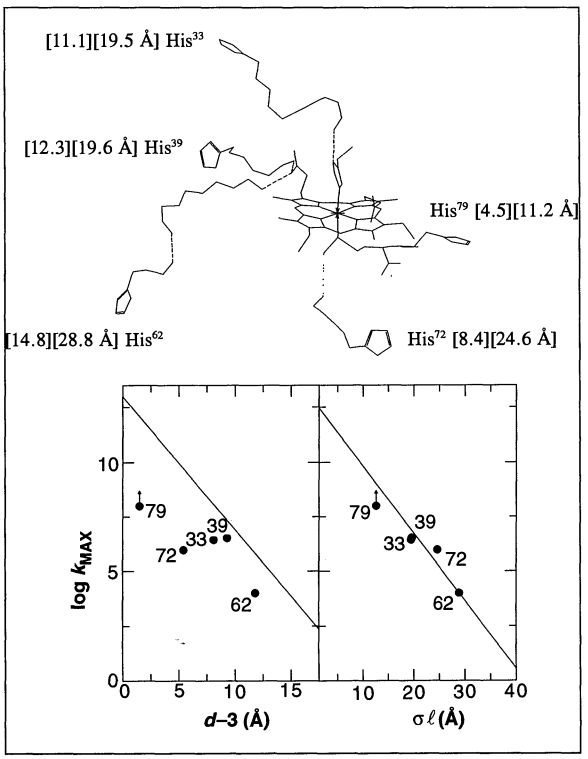

Fig. 1. (Upper) Electron-tunneling pathways in Ru(His^X)-modified cytochromes c (*2*). Edge-edge distances and tunneling path lengths are indicated in brackets ([*d*][σℓ]). **(Lower)** Correlations of activationless ET rates in Ru(His^X)-modified cytochromes with *d* and σℓ.

T_{DA} drops by a simple multiplicative factor ε as the chain is lengthened (*5*). The factor ε depends on the energy of the tunneling electron as well as on the composition of the repeat unit in the bridge. For simplicity, the decay can be divided into components associated with each bonded and nonbonded contact within the repeat unit.

A tunneling-pathway model for electronic coupling in proteins has been developed by generalizing the foregoing periodic-system model (*5*). Tunneling is much more efficient (decays more slowly) through bonded orbitals than through space because the effective potential barrier is lower. In proteins, the covalently bonded path between donor and acceptor can be extremely long compared to the direct through-space distance. In the pathway approach, the protein structure is analyzed for the combination of bonded and nonbonded interactions that maximizes T_{DA}. The tunneling pathways obtained contain mostly covalent and hydrogen bonds, with

D. N. Beratan is in the Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260. J. N. Onuchic is in the Department of Physics, University of California, San Diego, La Jolla, CA 92093. J. R. Winkler and H. B. Gray are at the Beckman Institute, California Institute of Technology, Pasadena, CA 91125.

occasional through-space jumps. A key realization was that the coupling decay across a hydrogen bond was approximately equivalent to that across two covalent bonds (*5*). This prediction has been confirmed in both small molecules and proteins (*6*, *7*).

Cytochrome c

The 1DSB model for protein ET predicts that ln k_{ET} should scale linearly with donor-acceptor distance. In the pathway model, rates should scale with the product of decay factors for each step in the pathway. Thus, if pathways between donor and acceptor consist of a small number of strong links (covalent or hydrogen-bonded connections), the couplings and the rates will be unusually large. However, if a donor-acceptor pair with the same separation distance has circuitous bonded pathways (large number of covalent or hydrogen-bonded links) or weak direct paths (long or numerous through-space contacts), the rate will be relatively slow. These qualitative expectations can be quantified by calculating the effective tunneling pathway length, $\sigma\ell$: Figure 1 shows that ET rates drop exponentially with $\sigma\ell$ (but not with direct donor-acceptor distance) in ruthenium-modified cytochromes c (*6*).

Dutton and co-workers (*8*) recently suggested that the uniform 1DSB model for electron tunneling with $\beta = 1.4$ Å^{-1} describes a broad range of natural and synthetic ET systems. While Dutton's fit to a single exponential does capture the approximate exponential decay of rates over 12 orders of magnitude (20 Å), it is unsatisfactory when examining individual subclasses of ET reactions, such as those in cytochrome c. Comparison of the experimental data to Dutton's line (Fig. 1) reveals discrepancies of several orders of magnitude for some points. The 1DSB model captures the overall decay of coupling for a very large range of distances and rates and agrees with pathway models in the average values of β (although different proteins are expected to have different average β values). The pathway analysis suggests, however, that the structure of the intervening protein medium is absolutely critical in determining the rates of individual protein ET reactions.

Pathways of protein complexes

While photosynthetic ET reactions occur between redox sites embedded in a single protein, many ET events are bimolecular. There is considerable interest in dissecting the docking, low-dimensional diffusion, and activated ET steps that occur in bimolecular ET processes. Indeed, the complex ET kinetics found for cytochrome c–cytochrome c peroxidase complexes may be a reflection of these factors (*9*–*11*). Although all of the pathway issues discussed above apply to bimolecular reactions, we generally know less about the geometry of the complex and which processes are rate limiting.

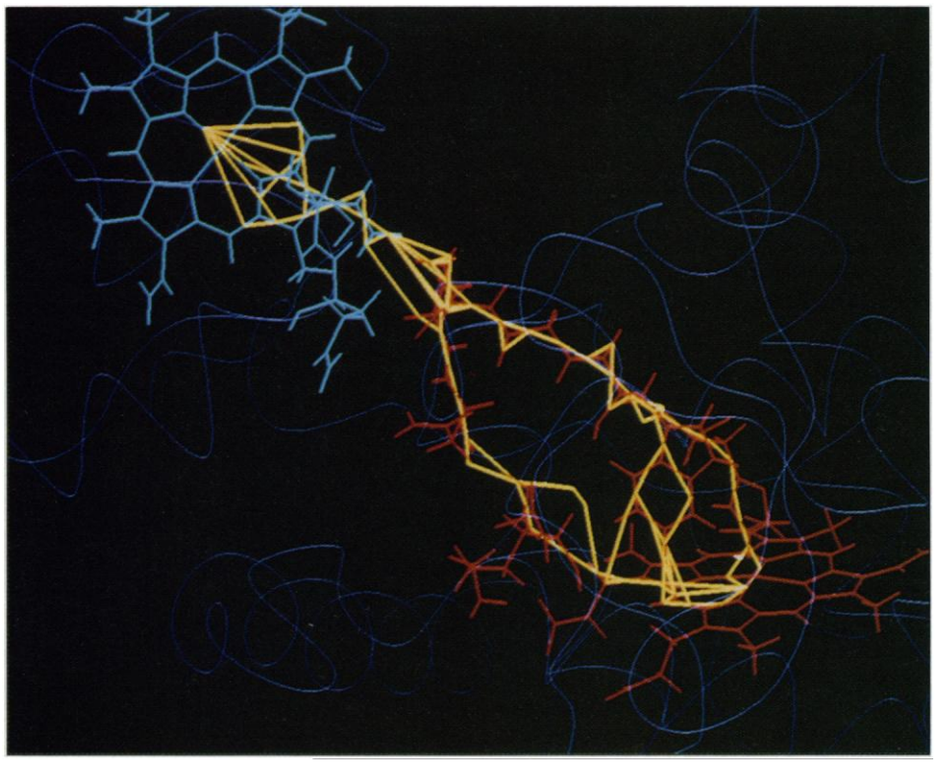

Fig. 2. Electron-tunneling pathways for the yeast cytochrome c–cytochrome c peroxidase complex: blue, cytochrome c heme; red, cytochrome c peroxidase heme and pathway residues; yellow, three families of pathways that dominate the electronic coupling [the PK path (1) is the upper one through Trp^{191}]. Pathway calculations were performed with the PATHWAYS II software package; the software and user's manual are available from J. Regan at jeffr@tucano.ucsd.edu.

In prior crystallographic studies of the cytochrome c–cytochrome c peroxidase complex, only disordered phases were found (*12*). The Pelletier-Kraut (PK) work (*1*) at both low-salt (horse heart cytochrome c) and high-salt (yeast cytochrome c) concentrations reveals remarkably similar docking sites despite differences in the intermolecular interactions likely associated with salt concentration. A pathway along the cytochrome c peroxidase backbone was proposed to be physiologically relevant on the basis of the crystal structure (*1*). Calculations of the high-salt structure indicate that three distinct families of pathways dominate the electronic coupling (Fig. 2). Although the PK path (1) gives the strongest coupling, the other two pathway families are just a factor of three or four weaker. We also find significantly different coupling strengths between the high- and low-salt structures. This difference highlights the importance of intersubunit contacts in mediating electronic-coupling interactions.

We are approaching a degree of sophistication in our theoretical understanding where we will soon be able to classify secondary and tertiary protein structural motifs with respect to their electronic mediation properties. This will include the relevance of multiple pathways and constructive or destructive interference within a given motif. And our understanding of protein-protein docking and ET is being advanced rapidly by the structure determinations of biological ET complexes such as cytochrome c–cytochrome c peroxidase (*1*).

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