Commentary

Dynamics and function of proteins: The search for general concepts

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For an understanding of the phenomena, the first condition is the introduction of adequate concepts; only with the help of the correct concepts can we really know what has been observed. When we enter a new field, very often new concepts are needed, and these new concepts usually come up in a rather unclear and undeveloped form. Later they are modified, sometimes they are almost completely abandoned and are replaced by better concepts which then, finally, are clear and well defined.

Werner Heisenberg (1)

Proteins execute and control essentially all functions in living organisms, and they do it elegantly and efficiently, with designs honed by billions of years of evolution. For each protein, we can ask how it performs its specific function. Because there are at least 100,000 different proteins, all important for life, the task to study, characterize, and understand all proteins will take a very long time. There may, however, be a complementary approach to the problem, namely to find general concepts, properties, and laws that characterize proteins and other biomolecules and that may lead to shortcuts in understanding newly discovered systems. The work of Réat and collaborators, demonstrated that the mean-square displacement of the active center in Mb is smaller than that of the protein overall. The results obtained on BR and Mb were thus similar.

X-ray light sources, detectors, and computers have improved dramatically since the early Mb data were taken. As a result, the resolution has improved and the Debye-Waller factors are determined more reliably. Fig. 1 presents the structure of sperm-whale Mb, with O₂ bound at the iron atom in the heme center. The colors denote the $<x^2>$ ranges, where $<x^2> = <u^2>/3$. The figure shows that $<x^2>$ generally is smaller at the center than toward the outside of the protein, but it also indicates that there are directions that appear to be less rigid than others, thus suggesting where entrance and exit channels could exist (7). The data and the figure refine the notion introduced earlier that the center of Mb can be called an aperiodic solid, whereas the outside is semiliquid (8). The average backbone values of the mean-square displacements for Mb-O₂ and deoxyMb at 80 K are shown in Fig. 2 versus residue number. The arrows in Fig. 2 indicate the five conserved residues (Leu-29, Phe-43, His-64, Val-68, and Ile-107) that surround the bound oxygen molecule, and His-93, which is bound to the iron atom on the proximal side of the heme group. These residues have small values of $<x^2>$, allowing specific control at the active site. Fig. 2 also shows that most residues on the proximal side of the heme group or far from the heme center have large mean-square displacements, just as was found for BR. The two figures demonstrate how the improvements in technique have led to a deeper insight into where the protein is rigid and where it is flexible.

The fact that BR and Mb, two proteins with very different structures and functions, show similarities in their dynamic behavior leads back to the question asked at the beginning.

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atom on the proximal side.

heme pocket and His-93, which is covalently bound to the heme iron
form. Arrows indicate the five conserved distal residues that line the
residue at 80 K of sperm-whale Mb with oxygen bound, and the deoxy
structure determined by x-ray diffraction therefore has values
in different CS have slightly different structures and the overall
structure determined by x-ray diffraction therefore has values
of the mean-square displacements that are far larger than
expected if the atoms were only vibrating. At temperatures
below $T_g$, x-ray diffraction shows the frozen distribution,
whereas EINS gives no information about the existence of CS.
Above $T_g$, proteins can access CS that are higher in energy and
are not occupied below $T_g$. X-ray diffraction takes snapshots
of the expanded distribution, whereas EINS follows the jump-
ing nuclei from CS to CS. Both therefore see a broader
distribution above $T_g$. The concept of an energy landscape is
not only useful in the discussion of the dynamics of the folded
protein, it also enters the folding problem (13).

The preceding paragraph oversimplifies the description of
the energy landscape. It is actually organized in a hierarchy
of a number of tiers (14). Different tiers are characterized by
different heights of the average enthalpy barriers separating
the individual CS. Each CS in a given tier contains a number
of CS in the next lower tier, and so on. The functional
importance of the hierarchical organization is not yet known.
The existence of a hierarchy implies that each tier has a
different $T_g$ (15). This phenomenon is seen in figure 4 of
the paper by Réat et al. (2): the global $T_g$ is about 150 K, whereas
$T_g$ for the region near the active center is about 220 K.

In a normal glass, $T_g$ is essentially independent of the
medium that surrounds the glass. In a protein, however, $T_g$
depends on the surrounding, as observed in Mb (16–19) and
in BR (20). If, for instance, Mb is embedded in a glass, the
interconversion of the CS in some tiers is suppressed (18, 21).
The transitions in some of the tiers are “slaved glass transi-
tions;” their $T_g$ is closely linked to that of the solvent (22). This
linkage provides a mechanism for the control of protein
reactions by changes in its surrounding.

The concepts of a rugged energy landscape, conformational
substates, and slaved glass transition are recognizable in the
proteins studied in detail over broad temperature ranges and
with many tools. Are they, echoing Heisenberg, still unclear
and undeveloped or are they already clear and well defined?
More work of the type described by Réat and coworkers (2)
and undeveloped or are they already clear and well defined?
More work of the type described by Réat and coworkers (2)
on more proteins is needed before a final answer will be available.
In particular, much work will be needed to establish a clear
connection between structure, dynamics, and function. Figs. 1
and 2 suggest that a study of the mean-square displacements
in mutants could lead to a better understanding of how to
design proteins with desired properties, for instance high-
temperature enzymes (23).

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2. Réat, V., Patzelt, H., Ferrand, M., Pfister, C., Oesterhelt, D. &


Applied Physics*, eds. Trigg, G. L., Vera, E. S. & Greulich, W.

754–756.


(London)* 280, 558–563.

79, 4967–4971.

331–371.

11. Frauenfelder, H., Bishop, A. R., Garcia, A., Perelson, A., Schus-
ter, P., Sherrington, D. & Swart, P. J., eds. (1997) *Landscapes:
Paradigms in Physics and Biology: Concepts, Structures, and
Dynamics* (North–Holland, Amsterdam).

254, 1598–1603.
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