MUTATION–ABSORPTION MODEL OF THE ENZYME

Michael Conrad
Department of Computer and Communication Sciences,
University of Michigan,
Ann Arbor, Michigan 48109, U.S.A.

Gradual changes in function of proteins in response to single changes in primary structure are often observed to occur and are a necessary condition for evolution by variation and natural selection at the protein level. A probabilistic (entropy theory) analysis of the effect of changes in primary structure on three-dimensional shape and function shows that such gradualism is based on the presence of a control system in the molecule involving a definite general form of structure-function degeneracy. The assumptions of the analysis are that primary structure determines tertiary structure (or a thermal distribution of tertiary configurations and allosteric forms), tertiary structure determines function (characterized by rate and other parameters), and that certain features of tertiary structure may be specialized for particular functions. The main conclusion is that embodied in the molecule is a subsystem which serves as a buffer, absorbing mutation or other forms of genetic variation and expressing these as graceful variations in features of the shape critical for function. This buffer system may be realized by numerical redundancy of amino acids or other mechanisms which increase the redundancy of weak interactions responsible for folding, utilization of amino acids having a greater number of analogs with redundant features, or local and global structural formats which allow for more effective utilization of redundancy. The mutation–absorption model has implications for the interpretation of structure–function relations in biology, the topology of the adaptive landscape, the interpretation of isoenzymes and allozymes, the relationship between selection and neutralism in evolution, and the relation between the complexity of and energy required by biological systems and the effectiveness of evolutionary optimization.

1. Introduction. Central to the study of enzymes and proteins generally is the idea that function is implicit in tertiary structure and tertiary structure is implicit in primary structure (or amino acid sequence). For the evolution of proteins, however, an additional consideration is of fundamental importance. This is that shape and function must in many cases change only gradually with single changes in the primary sequence. The argument is that if this were not the case each protein would be isolated atop some
adaptive peak, with no easily traversable pathways for reaching other adaptive peaks (cf. Maynard-Smith, 1970). The simple probabilistic consideration underlying this argument is that the probability of jumping from one adaptive peak to another in a single step depends on the product of probabilities of all the independent genetic events required for this jump; whereas the probability of moving from peak to peak in a series of single steps is in essence additive (Conrad, 1972a).

In this paper an attempt will be made to develop a conceptual model of structure–function relations in the enzyme based on the above consideration, viz. on the consideration that it is on a gradualistic relation between function change and primary structure change that all protein evolution depends and therefore that this relation must be the decisive historical influence on macromolecular structure–function relations. From this point of view there must be added to the list of functional properties of the enzyme the function of contributing to amenability to the evolution process itself. This evolutionary function may be described by studying the effect of primary on tertiary and hence on functional variability, the object being to determine the conditions under which mutational events at the primary level are most likely to appear as slight changes in some feature of shape critical for function and therefore in terms of slight changes in function. The model which emerges may be called a mutation–absorption model since its essential feature is that implicit in the protein structure is a buffer system which absorbs mutations and expresses them gracefully in terms of slight changes in those features of three dimensional shape critical for the conventional functions, e.g. rate processes, binding, mobility, cooperativity, control, structure formation. According to the mutation–absorption paradigm the structure of the enzyme cannot be interpreted solely in the framework of these conventional functions.

2. Determinate Relationships between Primary and Tertiary Properties. Among the various aspects of enzyme structure and function certain quite definite relationships are generally believed to obtain:

(i) **Folding relation.** Primary structure determines tertiary structure (three dimensional shape), or more precisely a (thermal) distribution of possible tertiary structures in a given milieu and (in some cases) under given initial conditions.

(ii) **Lock–key relation.** Tertiary structure determines function (characterized by various rate constants, binding constants, etc.).

(iii) **Function–environment relation (allosteric property).** Enzymes are capable of undergoing shape (and therefore function) changes in response to the substrate or to control chemicals in the environment.

(iv) **Functional specialization.** Certain features of the tertiary structures