Linked functions

Gary K. Ackers

Binding and Linkage: Functional Chemistry of Biological Macromolecules. By Jeffries Wyman and Stanley J. Gill. *University Science Books, Mill Valley, California 94941, USA/WH Freeman: 1990. Pp.330. $48, £31.95.*

Rummaging around — a town's debris is encountered by a polar bear on its migration route in Canada. Taken from *Into Harmony with the Planet: The Delicate Balance Between Industry and the Environment* by Michael Allaby published by Bloomsbury at £14.99.

BIOLOGICAL macromolecules such as proteins and nucleic acids 'make their living' by forming highly specific complexes with other macromolecules, and small molecular species (for example, enzyme substrates), or by changing their shapes in response to environmental 'signals'. Regulatory effects arise when two or more of these processes exert mutual influences on each other, with the macromolecule acting as a transducer of free energy. The Wyman theory of 'linked functions' provides a predictive framework for understanding these mutual influences — a kind of 'molecular sociology', as Jeffries Wyman has enjoyed calling it during the past four decades. The power of Wyman's conceptual approach is exemplified by its application to the Bohr effect on haemoglobin, a linkage between the two functions of oxygen binding and proton binding (or release). From an experimentally measured number of protons that are released by the haemoglobin molecule upon binding four oxygens, the exact change in oxygen affinity with changes in pH can be predicted. Analogous relationships can be deduced for linked functions in biological macromolecules of every class, including allosteric enzymes, repressor/operator gene control complexes, and membrane receptors.

What makes linkage theory work is a set of special relations (such as the Gibbs-Duhem equation) between the classic thermodynamic potentials. Wyman's ideas, like those of G. N. Lewis, are a creative and powerful extension of these fundamental relationships and should have widespread applicability to biochemical systems. But the linked-functions approach has been under used by researchers and under-taught to research students in spite of a few well-publicized successes such as the haemoglobin case cited above. This is partly attributable to the inherent subtlety and difficulty of thermodynamic reasoning (often not helped by an uninspired exposure of students to the basic subject), and partly to the fact that Wyman's major writings on the subject were frequently opaque to all but the most avid devotees who would take the trouble to decipher the seemingly cryptic, but ultimately practical equations. Thus although the importance of thermodynamic linkage has been recognized by many, its actual understanding has been achieved by only a few.

Binding and Linkage is a refreshingly readable monograph that will be useful both to graduate students and more senior researchers. The first three chapters provide a clear introductory background to the more advanced theory covered in later chapters. Because structure-energy correlations lie at the heart of mechanistic understanding, a gallery of macromolecular structures is presented at the outset to illustrate the organizational levels and types of functionally related interactions of interest. Although linkage relationships apply, in principle, at any level of structural detail, the theory has special advantages when the interacting subsystems are larger than atomic scale. Applications are thus focused on processes such as the associations between whole subunits (with their sometimes dramatic influence on the binding of ligands), the energetic coupling between conformational 'melting' of intramolecular domains, and the mutual coupling between ligands which bind at widely separated sites on the same macromolecule. Using linkage relationships, it is feasible to decipher the rules of functional coupling for molecules so large that atomic-level details are inaccessible or mechanistically uninterpretable. Illustrative examples of linkage phenomena are presented throughout the book from work by numerous authors, including highly significant contributions from Stanley Gill's own research, and from collaboration between Wyman and Gill.

A unique feature of *Binding and Linkage* is the retrospective (in chapter 4), of Wyman's contributions to the early ideas of allosteric regulation. Two mechanistic lines of thought emerged in the attempts to understand cooperativity of haemoglobin oxygen binding and related effects in multi-subunit enzymes. The 1935 model of Linus Pauling, and subsequent extensions by D. Koshland in the 1960s, used the concept of ligand-induced conformation changes of individual subunits, which produced nearest-neighbour interactions within a multimeric protein structure. This 'sequential' concept was also advanced by J. Monod and his associates at the Institut Pasteur in their original (1963) allosteric model. The second, sharply contrasting concept had been proposed by Wyman as early as 1948. Wyman assumed a 'pre-existing equilibrium' between alternative conformational forms of the haemoglobin molecule, with preferential binding of ligands to one of them. This 'concerted transition' concept was incorporated into the famous 'MWC model' paper of 1965, which Monod coauthored with Jeffries Wyman and Jean Pierre Changeux. The crystallographic structure work of Max Perutz, along with numerous solution studies on haemoglobin, have demonstrated unequivocally the existence of two major conformations of the tetrameric molecule with switching properties that have validated Wyman's early conjecture.

Binding and Linkage is much more than a retrospective of the conceptual contributions of Jeffries Wyman to the understanding of regulatory mechanisms in haemoglobin. The later chapters discuss major new ideas and developments of the last decade, and point the way to areas of theory that require additional development. This book offers a very practical set of tools for the experimental biochemist, and also a series of deep insights into the fundamental energetic constraints wherein biological systems must do their functional business. □

Gary K. Ackers is in the Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, Missouri 63110, USA.

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