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Is symmetry conservation an unessential feature of allosteric theory?

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The role of symmetry in allosteric theory is historically and philosophically revisited. The (at least approximate) symmetry of the hemoglobin binding curves led investigators to postulate a similar symmetry or equivalence in the binding sites, which meant a symmetrical arrangement of the hemes and of the whole molecule. Later Monod introduced the concept of symmetry conservation to describe allosteric behaviour. It is shown that this postulate does not really belong to the framework of allosteric theory as it was developed in thermodynamical terms. Symmetry, however, still plays a role at several levels in the underlying mathematical theory of binding and linkage in biological macromolecules.

1. Introduction

In the famous Monod-Wyman-Changeux model of allosteric behaviour, Jacques Monod introduced the idea of structural symmetry conservation as an essential feature of oligomeric proteins when they undergo allosteric change [1]. In later models, such as the Koshland-Nemethy-Filmer model, the existence of structural asymmetric intermediates was shown to be a key to allosteric mechanisms [2]. According to this model, protein subunits may exist in different conformations independently of the state of the neighbouring units. Moreover, in larger multi-unit structures, it is difficult to imagine how symmetry conservation holds true. The purpose of this paper is to make historical and philosophical comments on the role of symmetry in the allosteric picture and on the various levels, structural or formal, at which it may or may not intervene.

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2. Jeffries Wyman's hemoglobin studies prior to the MWC model: how to interpret the symmetry of binding curves

The allosteric behaviour of biomolecules was first described by Jeffries Wyman as early as 1951 in his study of heme interactions in hemoglobin [3]. The basic concept of entropy changes as a result of hemoglobin oxygenation was established by the analysis of thermo-chemical data. The entropy changes were assumed to reflect structural changes within the hemoglobin molecule. The details of these changes were impossible to grasp at that time. When the hemoglobin molecule was dissociated into dimers in concentrated urea solutions, oxygenation of the second heme seemed to be easier than of the first (but this idea of dimer cooperativity has since been abandoned). Thermodynamical analysis showed that the difference in free energy between the two reactions was entirely due to entropic factors.

Interestingly enough, symmetry came into the picture within this argument. When compared with Perutz's crystallographic results, which gave only a rough picture at that time, entropy variations seemed to reveal a change from a less ordered to a more ordered, more symmetrical conformation. This part of the argument was based on less valuable grounds than the purely thermodynamical reasoning. Nevertheless, the increase of symmetry in the course of such a complex physicochemical reaction is not an entirely irrational idea. It is compatible with Curie's principle, which prohibits the spontaneous generation of asymmetry and allows an increase of symmetry to occur in physical effects, because of the weakness of some asymmetric causes.

The symmetry argument has its roots in Jeffries Wyman's previous phenomenological studies on the binding properties of hemoglobin. In these studies, symmetry had already come into the picture in a more fundamental way. The oxygen binding curves of hemoglobin appeared to be (at least approximately) symmetrical. When he investigated the symmetry conditions of these curves – long before the allosteric concept was proposed as a key to cooperative behaviour – Jeffries Wyman recognized that the observed symmetry could be explained on the basis of the identity of binding sites [4]. This result was obtained during the investigation of heme interaction, a concept which had been previously proposed by G.S. Adair and L. Pauling in their explanation of cooperative effects in hemoglobin.

What was meant by heme interaction was Pauling's following assumption: the binding properties of hemoglobin shown by the curves can be explained by a model in which only two equilibrium constants are used, the constant of the free energy change accompanying the addition of oxygen to heme, and an additional constant for the free energy change which goes with the oxygenation of two adjacent hemes. Hemes were supposed to be close to each other and to interact in pairs, along the sides of a square. The hemes and their interactions were supposed to be equivalent [5]. Clearly, symmetry was present in the postulates of hemes equivalence and interactions: the hemes were supposed to be physically indiscernible.

In his 1948 review on heme proteins, Jeffries Wyman wrote: "The problem of elucidating the nature of the interactions between the four hemes is considerably simplified if...we accept the idea of the inherent identity of the four oxygen-combining centers, as we shall do tentatively at least" [6]. In order to establish this point, one has to investigate the symmetry conditions and properties of the binding curves. The essential condition is that the reactive groups should be 'indistinguishable' in their mutual relations. However, an examination of recent data led Jeffries Wyman to modify somewhat Pauling's square model: the binding curves showed elements of asymmetry, and data on hemoglobin dissociated in urea showed a high interaction energy within the dimer.

This last result means that the interactions are stronger within the heme pairs than between them: the symmetry elements of the molecular structure are thus lower than expected – a fact strikingly confirmed by Perutz's crystallographic results [7]. But this circumstance did not lead to any asymmetry property in the binding curves. In order to explain their slight asymmetry, Jeffries Wyman assumed that the interaction energies were not simply additive, and that a more complicated pattern of interaction occurred within the hemoglobin molecule.

The problem of heme equivalence and symmetry was further discussed, with the help of new methods and data, in 1950. Commenting on Perutz's studies, which revealed the cylindrical shape of the molecule, Jeffries Wyman pointed to the existence of a two-fold axis of symmetry perpendicular to the cylinder axis, the four hemes occurring in pairs and their planes being parallel to the two axes. He wrote: "These conclusions are in good agreement with inferences based on quite a different set of considerations involving the physicochemical behavior of hemoglobin" [8]. In view of the whole phenomenological evidence, Jeffries Wyman was fairly confident at that time that symmetry was a 'fundamental feature' of the equilibrium curves, revealing not only the equivalence of the hemes, but also of the heme-globin configurations [9].

In view of the fact, later discovered, that two types of globin chains are present in hemoglobin, and, what was already more firmly established, that some asymmetry is still present in the curves, the conclusions which could be reached at that time were later modified. In 1982, Gregorio Weber pointed out that the real asymmetry of the binding curves should be explained by asymmetric interactions between the subunits within the hemoglobin molecule. He was led to do so by a rigorous use of the second part of Curie's principle, "when certain effects reveal a certain asymmetry, this asymmetry has to be found in their causes" [10]. In a way, the whole previous hemoglobin story is a comment on this point, since it was an attempt to relate the symmetry properties of the effects to the symmetry of the causes.

3. Symmetry conservation in allosteric change

From the viewpoint of symmetry, Monod's allosteric concept did not introduce any new fundamental ideas, compared with the preceding investigations; rather it was, in a way, a throwback. In the 1964 MWC model, Monod set the postulate of *structural* symmetry conservation as an essential feature of allosteric change. This statement was only partly inspired by Perutz's detailed crystallographic data on oxy- and deoxyhemoglobin conformations. It can be considered as a theoretical effort to explain the molecular mechanisms of allosteric change on the basis of physical principles. Perhaps this effort was guided by the feeling of an analogy with the most basic principles of physics, like the invariance principles and the symmetry conditions. There is indeed a definite and at least literal analogy between Monod's statement and Curie's famous statement, that the same symmetry elements in the causes must be found in their physical effects. How far philosophically does this analogy lead? Is it only superficial, or does symmetry still play a role, although at a deeper level than Monod could imagine, in the allosteric picture?

Monod's ideas raised several criticisms from prominent molecular biologists, who rightly pointed out that the symmetry conservation statement was a naive and unnecessary part of the model; its theoretical strength resided rather in the kind of formalism developed to describe cooperativity. Indeed, the symmetry conservation statement does not address the symmetry conditions in the creation of a physical effect, which represent the real meaning of the symmetry principle as rightly used in the previous investigations on hemoglobin. Rather, it addresses the existence of two stable structures of an oligomeric molecule under slightly different physico-chemical conditions. The symmetry elements of the molecule are deduced by topological arguments for monomer associations in closed structures. Symmetry enters the picture in the way the oligomer is constructed. Symmetry conservation is only a corollary of the stability conditions for these structures.

In order to investigate better the different meanings of symmetry conservation from the viewpoints of both Monod and Curie, and their different philosophical depth, we first have to go back briefly to Curie's fundamental ideas and to the kind of evidence on which they are based.

4. Pierre Curie on symmetry in physics

Curie's views on symmetry can be summarized in two statements: the symmetry elements of the causes must be found in their effects, the asymmetry elements of the effects must be found in their causes. As a consequence of this, symmetry may increase in physical effects. This corollary of Curie's principle has not been borne out, since spontaneous symmetry breaking occurs in physics. As to the kind of evidence on which these ideas are based, Curie pointed out that the symmetry elements of an electric and a magnetic field are not identical. The study of the symmetry elements is exemplified in the way in which Pierre Curie derived the symmetry properties of a magnetic field from the symmetry properties of its cause, an electric current in a circular wire.

In his famous paper 'On symmetry in physical phenomena', Curie does not start from symmetry but from asymmetry. A certain asymmetry is necessary in order to create a physical effect. The asymmetry of a physical medium has definite consequences on the effects which can be created within this medium [11]. Judging the characteristics of the medium in terms of symmetry rather than asymmetry is only a change of viewpoint, which is advisable simply because it is possible to define mathematically symmetry elements and groups, rather than asymmetry elements, which are infinite in number.

Having defined several of these symmetry groups, Curie continues with some other statements. The characteristic symmetry of a phenomenon is the highest degree of symmetry compatible with its existence (or the lowest asymmetry). A phenomenon may exist in a medium which has the characteristic symmetry of the phenomenon or the symmetry degree of one of the (lower level) intergroups of its characteristic symmetry. In other words, Curie goes on, certain symmetry elements may coexist with certain phenomena, but they are not necessary. What is necessary is that certain symmetry elements do not exist. It is asymmetry which creates the phenomenon [12]. Curie's fundamental statement is about asymmetry and its role in physical effects.

One of the obvious consequences of these statements is that when certain effects come into combination, the characteristic magnitudes of the physical medium which are additive are the asymmetry elements. As to the symmetry elements, there only remain the (lower level) elements which are common to both phenomena [13]. In this way, the symmetry conservation statement, which tells that the symmetry elements of the causes must be found in the effects, is only a corollary of Curie's fundamental statement about asymmetry. It means that the symmetry elements which are common to the various causes and which characterize the physical system are the ones of the medium in which the effect is going to take place. With the help of these symmetry elements we can calculate the structure of the effect, which is really governed by the lowest asymmetry of the medium.

Curie continues saying that the reciprocal of these statements is not true, at least practically. This means that symmetry may increase within a physical system, because certain asymmetry elements may have no significant effect on certain phenomena. As is well known, this part of Curie's argument does not hold true, since spontaneous symmetry breaking may occur in physical systems. The theoretical physicist Louis Michel recently proposed that the natural occurrence of spontaneous symmetry breaking, which is commonly considered as a violation of Curie's principle, suggests that 'physical laws might have more symmetry than physical states' [14].

There is perhaps irony in the fact that the most widely known of Curie's statements pertains to symmetry, whereas his main idea pertains to asymmetry or, in more modern terms, broken symmetry. These ideas are nevertheless complementary, since symmetry elements are conditions for laws, whereas asymmetry conditions create an effect within the structure designed by symmetry laws (this again would pose the problem of the symmetry elements of laws compared with those of states or events).

5. Hermann Weyl on symmetry and causality

As is well known, symmetry now plays a major fundamental role in the theoretical framework of contemporary physics, because of its usefulness in the derivation of physical laws. In his epistemological writing, *Philosophy of Mathematics and Natural Science*, Hermann Weyl, who widely used symmetry in his attempt to formalize quantum mechanics by the theory of groups, considered the symmetry principle as a statement which could be used in simple cases to establish laws. One of these cases is Archimedes' theory of the lever, which begins by the proposal that equal weights at lever arms of equal length are in an equilibrium state. The key to this statement is the notion of symmetry or mirror image, since the system's whole configuration remains unchanged on reflection [15]. More generally, as was demonstrated in a famous theorem by the German mathematician Emmy Noether, there is a definite relationship between the idea of symmetry or invariance and the conservation laws of physics.

Weyl also considered the symmetry principle as a mathematical equivalent of the principle of sufficient reason, because of the connection of symmetry conservation with the idea of causality. Indeed, the principle of sufficient reason is not only a statement about the necessary causality of every event, but also a statement about a common measure of cause and effect, the cause to be considered being the smallest one compatible with the existence of the effect (this would be the meaning of the word 'sufficient'). In this way, Curie's statement about the asymmetry elements of the effects, which are to be found in the causes, may be rigorously considered as one of the forms which the principle of sufficient reason might take [16]. It means that there is no effect without a cause. The other statement, that the symmetry elements of the causes must be found in the effect, allows rather a mathematical treatment to be used in the search of the effect and its properties (e.g., the symmetry elements of a magnetic field created by an electric current). On the whole, Curie's statements result from the combination of the principle of sufficient reason, with the idea that asymmetry creates physical effects, and with the theory of symmetry groups.

6. The meaning of symmetry conservation in the Monod-Wyman-Changeux model

If we now return to the allosteric picture, we may address the question of whether there is any reason why we should think of allosteric change as a process governed by something like a symmetry principle. The last of the statements which describe the MWC model reads as follows: 'When the protein goes from one state to another state, its molecular symmetry (including the symmetry of the conformational constraints imposed upon each protomer) is conserved' [17]. The protein is assumed to oscillate continuously between two equally symmetrical conformational states, which are endowed with different affinities for the ligand. The basic idea of the model is the idea of conformational equilibrium. The cooperative binding of ligands, homotropic or heterotropic, might be considered as the 'effect', the basic conformational equilibrium and its displacements along with the physicochemical properties of the surrounding medium as the 'causes'. The cooperative effect produced by increasing oxygen pressure is really created by the shift of the equilibrium in favor of the higher affinity conformation.

If the symmetry principle might be used here, it would thus help to explain the relationships between the phenomenological properties of ligand binding and the molecular phenomena which govern it. If we prefer to use the symmetry conservation principle to describe the conformational equilibrium as something like a physico-chemical process, we are faced with the troublesome question of deciding which is the 'cause' and which the 'effect' in the process – a rather unresolvable question. Monod's symmetry conservation statement is only a corollary of stability properties for oligomeric proteins. The real theoretical strength of the MWC model resides elsewhere: it resides in the statistical and thermodynamical understanding of cooperativity, an understanding clearly prepared by Jeffries Wyman's previous discussions on oxygen binding to hemoglobin and on the statistical theory of polyfunctional macromolecules.

Nevertheless, Monod repeatedly stated that the properties of the model are entirely due to reasons of symmetry [18]. Indeed, the microscopic dissociation constants of the various binding sites for a given ligand are assumed to be identical, by reason of symmetry, in each conformational state. However, structural symmetry is only the most apparent, most superficial feature which helps us to understand binding sites' identity. Instead of being implied by symmetry reasons, the assumption of binding sites' identity is a basic assumption, which allows the statistical treatment of the model to take place and is needed to explain fully in terms of thermodynamical theory the cooperative behaviour. The postulate of binding sites' identity, which we have already met in several guises in Pauling's and Wyman's previous studies, is a fundamental feature of the model. As a postulate of indiscernibility, it is perhaps its deepest rational basis. Identity, and indiscernibility, mean symmetry in a more abstract sense than Monod's idea of structural symmetry conservation. Cooperative behaviour and identity of the sites are in sharp contrast. Both the appealing character and the theoretical strength of the MWC model reside in the way in which these contrasting features are reconciled.

7. The problem of symmetry conservation in multi-unit structures

The questions of the theoretical value and empirical truth of Monod's symmetry conservation statement must be separated. As a matter of fact, symmetry conservation is largely exemplified in oligomeric proteins when they undergo allosteric change. As Max Perutz recently pointed out, the reasons for this are topological and result from the theory of point group symmetry. More precisely, the changes in quaternary structure which conserve the symmetry of oligomers and the equivalence of their subunits are mathematically defined, the motion of each subunit being related to the motion of the others by symmetry rules [19].

Does symmetry conservation hold true for larger multi-unit structures endowed with allosteric properties? Jeffries Wyman noticed that oxygen carriers like erythrocruorins and hemocyanins in invertebrates exhibit at the same time ordered structures and cooperative behaviour. Although it could be possible, in his view, to describe this behaviour in terms of the simple MWC model, it seemed more likely to him that mixed conformations play a role in these complex structures, thus departing from the stringent rules of the MWC model [20]. In a later study, A. Colosimo, M. Brunori and J. Wyman noticed that the oxygen binding curve of *Helix pomatia* hemocyanin could be fitted by the simple MWC model, with the assumption of 12 strongly interacting sites. This suggested, as a tentative explanation, the existence of structural domains or subgroups within the giant molecule, these subgroups being responsible for most of the cooperativity [21].

However, it has been shown in other hemocyanins that isolated domains bind oxygen in a non-cooperative way. The strong cooperative behaviour of these molecules should be ascribed to a change in their quaternary structure [22]. Even in such large multiunit structures, the occurrence of allosteric change without conservation of the overall symmetry is doubtful. As Perutz puts it,..., "most of Monod's predictions have been brilliantly borne out by the structural analyses... The subunit contacts of haemoglobin, phosphofructokinase and aspartate transcarbamylase are very clearly designed to allow only concerted transitions between alternative quaternary structures" [23].

But according to Perutz, the postulate of binding sites' equivalence and of microscopic dissociation constants' identity, which belongs to the theoretical framework of the MWC model, has not been entirely confirmed in the case of hemoglobin, since the oxygen affinity of any one subunit in the T quaternary structure depends on the ligation state of the next subunit. In Perutz's view, the oxygen binding mechanism is sequential rather than concerted, a view which he has consistently maintained [24]. To the question as to whether cooperative behaviour can occur without allosteric quaternary change, the answer is positive, as shown equally by organic model compounds and immunoglobulins [25].

8. Symmetry, complexity, and the association of monomers

Monod's idea, that symmetry is maintained in the conformational equilibrium, could be understood in another less empirical way, in which Curie's principle could again appear. We may indeed consider the conformational equilibrium as a limiting case of phase transition, the transition from a 'polysteric' (as termed by Jeffries Wyman) to an 'allosteric' system. If we look at the transition from a polysteric system of free monomers to an allosteric system in which monomers are associated by weak interactions, and if we consider it as a phase transition, we may judge it from the symmetry standpoint. In this case the 'effect' is the associated structure together with its microenvironment, and the 'cause' the dissociated monomers in their liquid medium. Comparing the symmetry elements and groups of the effect and of the cause would show in this case a change in symmetry. Such a change in symmetry appears, for instance, in liquid-solid transitions, which are usually described, in the Landau fashion, as a symmetry breaking process: the ordered structure has less symmetry elements than the disordered one, which is the most symmetrical because of its isotropy (see ref. 26 *). Clearly enough, Monod did not look at things in this way.

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* This idea may seem rather paradoxical. But as Landau puts it, "the most symmetrical bodies are isotropic bodies, whose properties are the same in all directions; these include gases and liquids (and amorphous solids)".

A closely related way to understand the allosteric behaviour is to consider monomer assembly from the standpoint of thermodynamics, as Gary Ackers did in a long series of studies on hemoglobin. Ackers showed that the negative free energy variation in the assembly process of dimers into tetramers is due to different factors in the cases of deoxy- and oxyhemoglobin. The free energy variation is greater in deoxygenated than in oxygenated dimers. In the deoxygenated case, enthalpy and entropy variations are negative. In the oxygenated case, enthalpy and entropy are positive; the negative free energy variation is due to a large positive entropy factor [27]. The reaction may be said (perhaps improperly) to be 'entropy driven'. The change in sign of the entropy factor between the deoxy and oxy cases raises difficult questions concerning the mechanisms of both reactions. Indeed, various factors contribute to entropy variations, such as hydrophilic and hydrophobic interactions, conformational states, and internal vibrational modes. A possible interpretation of the difference in entropy change between the deoxy and oxy states has been tentatively put forward by Ackers: "the assembly of deoxy tetramers leads to a much greater reduction in vibrational degrees of freedom than occurs in the assembly of oxyhemoglobin. This might account for the large negative entropy and enthalpy observed" [28].

To interpret these observations in a broad theoretical and philosophical framework, we can introduce the concept of thermodynamical complexity. According to this concept, energetic complexity and entropy may be defined by the number of ways the different elements of a system may reach the various energy repartitions corresponding to a given equilibrium state. It is philosophically significant to emphasize that not only space but also energy features belong equally to this concept. The biophysicist Jacques Tonnelat pointed out recently that spatial complexity variations are only exceptionally independent of energetic complexity variations [29]. This make them measurable in thermodynamical terms. Thus, the general concept of thermodynamical complexity can be useful to interpret, at least in a qualitative way, some features in the thermodynamics of monomer assembly processes [30].

Monomer or dimer assembly means the creation of a more ordered state, of a morphology. The reduction in internal degrees of freedom resulting from assembly is such that it still allows certain variations in the distribution of the various parts of the molecular structure among certain energy levels. This limited degree of internal freedom is one of the keys to allosteric behaviour. In the general terms of thermodynamical complexity and creation of order, Ackers's results show that many factors contribute in several ways to the creation of ordered structures.

Global entropy may increase or decrease depending on these factors, among which the oxygenation state seems to be particularly significant. The study of assembly energetics indeed shows that assembly is easier for unoxygenated dimers than for oxygenated ones. In other words, the oxygen favours tetramer dissociation. Allosteric functioning is really the beginning of a dissociation process, controlled by the oxygen. Such a concept can be extended readily to polyphasic systems, like sickle cell hemoglobin. Jeffries Wyman and Stanley Gill have shown that linkage properties appear in such systems [31].

9. Symmetry and invariance in the thermodynamics of biomolecules

If we now turn away from the MWC model and from the underlying molecular mechanisms to the formal treatment of binding and linkage in biological macromolecules, symmetry enters the picture in a more fundamental way, as in other parts of physics, where it is deeply related to the invariance principle. This could be an illustration of the following statement by Eugene Wigner: "the laws of nature, that is, the correlations between events, are the entities to which the symmetry laws apply, not the events themselves" [32]. To which kind of invariance principle should we have recourse to explain the laws of binding and linkage in polyfunctional molecules, including their cooperative behaviour?

John Edsall noted that the idea of thermodynamical linkage arises from Willard Gibbs's memoir *On the equilibrium of heterogeneous substances* [33]. This is perfectly clear for such linkage relationships as the Bohr effect and its reciprocal in hemoglobin. Here, symmetry enters the picture in the way in which any linkage relationship is reciprocal. This state of affairs is a consequence of the general equilibrium condition and of the very concept of equilibrium, which again involves some kind of symmetry. In a sense, equilibrium thermodynamics involve a symmetry principle.

A new chapter has been recently added to the equilibrium thermodynamics of heterogeneous systems by Jeffries Wyman with his concept of binding potential, applied to the system of a macromolecule and its different ligands. Moreover, the generalized concept of a group of potentials further enlarges the theoretical framework of macromolecular systems. There is a definite analogy between the way Jeffries Wyman created a formal, algebraic theory of these groups of potentials and the purely mathematical way in which Willard Gibbs derived the set of thermodynamical functions.

These various potentials are suitable to describe a complex macromolecular system with several ligands; they are derived from each other by a set of algebraic transformations, the Legendre transformations. Legendre transformations form an abelian group, which has definite symmetry properties. These symmetry properties are clearly shown in the multiplication table of two or three transformations, each including two or three variables [34]. The group character and the symmetry properties are equally found in the set of potentials created by the transformations. In each of these potentials, symmetrical linkage relations are readily found; symmetry appears also between linkage relations belonging to opposite potentials. Such a generalization of symmetry in complex systems at thermodynamic equilibrium is philosophically meaningful: symmetry conditions, rather than asymmetry ones, govern the formal algebraic structures which include the various potentials, these potentials corresponding to as many viewpoints as there may be on the behaviour of a complex system. It remains to examine symmetry properties in non-equilibrium systems, and the laws from which these systems derive.

Thus, Jeffries Wyman's work helps us to understand better the symmetry properties which regulate the behaviour of complex systems in thermodynamical equilibrium, and perhaps also to realize that symmetry applies to laws in a broader and richer way than to physical structures.

Are the laws of nature more symmetrical than the events, processes, or structures? As Hermann Weyl forcefully demonstrated in his beautiful book *Symmetry* [35], symmetry is a group concept. A group concept applies to formal structures. Symmetry applies to laws. Such a group concept represents one of the highest and most powerful tools which we can use to unify our understanding of the world.

10. Postscript

It is perhaps not entirely unsuitable to the present circumstance to make more personal comments. These comments are not only a tribute to a pioneering work in the field of biophysical chemistry and an acknowledgement of its philosophical significance. They also could be a tribute to friendship, to its role in intellectual achievement and to human quality. When I first met Jeffries Wyman in Rome, he gave me a paper on symmetry, mainly devoted to the discussion of group symmetry in the family of potentials which may be derived by algebraic transformations from the energy or from the Gibbs free energy [36].

The history of protein chemistry has a special philosophical significance, in showing how chemical structure and biological function are deeply related (this topic has been developed in my book [37]). John Edsall was the first to draw attention to the special role of hemoglobin in this respect, in the historical development of biochemistry [38]. When I engaged in this part of the history of science, François Jacob recommended that I meet somebody in Rome. His advice paved the way to the Piazza Farnese. "Hemoglobin, that's my life", said Jeffries Wyman at once when I came to his home. I was soon to recognize that this was only half true. The other part of his life, his much regretted wife Olga, was perhaps as impressive as the whole hemoglobin story. Taken together, both parts represent an equally unusual combination of science and human values. Jeffries and Olga Wyman had a deep influence on those who had the privilege of knowing them.

The text on symmetry and its place in the study of biological macromolecules remind me of Jeffries' frequent walks in the gardens of Villa Doria Pamphili. The symmetry principle is largely exemplified in these gardens, but it is also moderated and underlined by many elements of asymmetry. The combination of richly symmetrical architectures and ever-changing, asymmetrical parts, the complementarity of stone buildings, trees and lawns creates a unique effect. In a way, the Villa Doria, like many other gardens of that time, has symbolic meanings. It is perhaps a symbol of the properties of living matter, of the tension between time and eternity, and of the task of biophysics, to which Jeffries Wyman still contributes enormously.

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