Holism and reductionism in biology and ecology

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CHAPTER 6
CO-OPERATING RESEARCH PROGRAMMES: REDUCTION OF THE BOHR EFFECT

6.1 Introduction

In this chapter I will illustrate my claim that holism and reductionism should rather be seen as co-operating and mutually dependent research programmes than as conflicting views of nature. I will do so by discussing a concrete example of heterogeneous micro-reduction in biology (which, for a change, doesn't come from genetics). The example concerns the reduction of a law in animal physiology which is called the Bohr effect and which pertains to the rates at which oxygen is taken up and released by the blood. I will show that this law has been reduced, with the help of the requisite bridge principles, to a theory of molecular biology, viz. the theory of allostery, and that this particular application of the theory of allostery has been reduced, again with the help of the requisite bridge principles, to the theory of chemical bonding. I will also show that at least six research programmes were involved in this reduction and that the relations between these programmes can be described perfectly in terms of the model of co-operating research programmes discussed in the former chapter. I have adopted the example from Rosenberg (1985, chapter 4), but the interpretation, in terms of reduction steps and co-operating research programmes, is mine.

6.2 Oxygen uptake by the blood

6.2.1 The Bohr effect

The example I will discuss is especially interesting because it pertains to one of the major life functions of life performances or organisms, namely their respiration. In the respiration of mammals (amongst others) oxygen is taken up from the environment by the lungs, absorbed by the blood and transported to the various tissues of the body, where it is used in energy producing reactions which allow the body to work properly and to perform actions. In the same reactions wastes are produced in the form of CO_2 molecules and hydrogen ions which are taken up by the blood and transported in the reverse direction to the lungs where they are breathed out.

At the beginning of this century the physiologists C. Bohr and J.S. and J.B.S. Haldane discovered that the rate at which oxygen is taken up and released by the blood is higher than one would expect on the grounds of simple diffusion, which would be determined only by the oxygen pressure, that is, the concentration of oxygen present. They discovered that the oxygen-binding capacity of the blood is determined not only by the oxygen pressure but also by the pH, that is, the concentration of hydrogen and CO_2. At high concentrations of these wastes (at the capillaries in muscle tissue) the blood releases oxygen more quickly than would be expected on the grounds of the oxygen pressure alone. And at the lungs, where CO_2 and hydrogen escape and where oxygen is present in surplus supply, oxygen is taken up more quickly by the blood. Thus, at high oxygen pressure and low acidity (high pH) (at the lungs) oxygen is taken up more quickly by the blood and at low oxygen pressure and high acidity (low pH) (at the capillaries) oxygen is released more quickly by the blood. This is called the *Bohr effect*.

These physiologists had discovered an important regularity, but they couldn't explain it. They couldn't explain why oxygen is taken up and released more quickly by the blood than expected. Thus, a problem was raised at the level of a physiological research programme

which could not be solved by that programme itself. The physiologists had no idea of the mechanism underlying the uptake and release of oxygen by the blood. The solution to this problem has come much later from the side of molecular biology. In the course of about three decades molecular biologists have succeeded, literally bit by piece, in solving the problem.

6.2.2 The role of hemoglobin

From *biochemical* research it was long known that the uptake of oxygen by the blood rests with the binding of O_2 molecules by iron atoms in hemoglobin molecules, which are proteins occurring in red blood cells. With the help of special analysis techniques, such as x-ray crystallography and electrophoresis, molecular biologists have been able, after decades of hard labour, to unravel the structure and composition of hemoglobin molecules. This allowed them to explain the Bohr effect.

Hemoglobin is a protein and like all proteins is made up of long chains of amino acids. It appears that a hemoglobin molecule consists of four sub-units, two of which are called α hemoglobin and the other two ß hemoglobin. Each of these sub-units consists in turn of two parts, a heme group and a globin molecule. A heme group is a relatively small molecule, a porphyrin molecule, containing an iron atom (to which an O_2 molecule can bind). A globin molecule is a long chain of approximately 140 amino acids which is bent and folded around the heme group in a specific, asymmetrical way. The difference between the α and ß sub-units lies in the nature of certain of the amino acids, but this is of no particular interest here.

It appears that the specific oxygen-binding properties of hemoglobin molecules, their *function*, is determined completely by their *form* and that this form is determined completely by the *nature* of the amino acids in the globin-chains, by the order in which they appear and by their *chemical properties*: whether they are positively or negatively charged and hence whether they attract or repel one another, whether they are hydrophilic (water soluble) or hydrophobic (not water soluble), and whether they contain smaller or larger sub-groups in their side-chains. In other words, once the identity of the separate amino acids is established - and this can be done with the afore-mentioned analysis techniques - it is possible from their properties and their order in the globin-chains to derive the complete, three-dimensional structure of the whole hemoglobin molecule. All one needs for this is the *theory of chemical bonding* (and information about the molecular milieu). With this theory it is possible to determine exactly where the globin molecules will bend, turn, overlap on themselves and come into contact with the heme groups and with each other such that the three-dimensional shape of the whole hemoglobin molecule results.

One may start picturing a globin molecule as a linear sequence of amino acids. In this form molecular biologists talk of the *primary structure* of hemoglobin. This is the form in which these molecules appear as a result of the chemical analyses and it is also the form determined by the genetic code on the basis of which hemoglobin molecules are synthesized.[39]

Besides this primary structure molecular biologists also distinguish a secondary, tertiary and

[39]There are presently 23 different amico-acids known. The nature of each of them is determined by a specific combination (triplet) of 3 nucleotides in a DNA strand. The total order of amino-acids in a protein (its primary structure) is determined by the total order of nucleotides in DNA strands that code for the protein's synthesis.

quaternary structure of hemoglobin. The *secondary structure* is the bent, twisted and folded structure of the globin-chains which result from the chemically possible covalent bonding angles between the separate amino acids. The *tertiary structure* is the shape of the molecule that results from intermolecular forces between amino acids that were far apart in the primary structure but are brought together in the secondary structure. The *quaternary structure*, finally, is the product of ionic bondings between amino acids in the four sub-units which result in them being packed together in the hemoglobin molecule as a whole. This too is determined completely by the properties of the amino acids and their order in the globin-chains, given, of course, a certain molecular environment. The quaternary structure is the eventual three-dimensional shape of a hemoglobin molecule and it is this shape that determines its specific oxygen-binding properties.

Before I go into those properties, it is of interest to point to a remarkable similarity in the hemoglobin molecules of different animal species. Although the hemoglobin molecules of all animal species differ in the order of most of the amino acids in their globin-chains, they are identical (homologous) in structure at nine of the approximately 140 amino acids per globin-chain. And it appears that just these nine amino acids principally determine the secondary and hence the tertiary and quaternary structure of hemoglobin as a whole. Substitutions can be found at all other positions in the primary structure (though not just any substitutions: one polar amino acid may replace another, or one hydrophilic amino acid may replace another), but at the nine points of the secondary structure where the primary structure begins and ends, bends, turns, overlaps on itself and comes into contact with the heme group, the amino acids of all hemoglobin molecules, within and across different animal species, are the same. Thus, it is principally to these nine amino acids that hemoglobin owes its three-dimensional shape and therefore its function (though of course the other amino acids are also required). These nine amino acids are 'conserved', as it is called. I will explain the significance of this later.

6.2.3 Allosteric effects

As mentioned, each of the four sub-units of a hemoglobin molecule has a heme group containing an iron atom to which a O_2 molecule can be bounded. Thus a total of four O_2 molecules can be bounded to one hemoglobin molecule. Now it appears that the binding of one O_2 molecule to one of the iron atoms in a hemoglobin molecule facilitates, and hence accelerates, the binding of three other O_2 molecules to the other iron atoms in the molecule. This phenomenon is called *positive co-operativity*. However, positive co-operativity is just another name for the phenomenon to be explained (the Bohr effect) and the question is therefore what the underlying mechanism is.

The theory with which molecular biologists can explain positive co-operativity is the *theory of allostery*. This theory was developed in the beginning of the sixties by Jaques Monod and his colleagues (Monod et al. 1963) to explain the specific activity pattern, the catalytic properties, of certain enzymes and other proteins. According to this theory, certain enzymes have two spatially separated bonding places called allosteric bonding places: one can be occupied by the substrate, that is, the substance which is regulated by the enzyme, and the other can be occupied by an inhibitor. The characteristic property of these enzymes is that the binding of the inhibitor leads to changes in the shape of the enzyme such that the binding of the substrate is prevented, and vice versa. These changes of shape are called *allosteric transitions*.

Such allosteric transitions appear to occur also in hemoglobin molecules. The substrate in this case is formed by O_2 molecules and the inhibitor appears to be a small molecule which was selected by Benesh and Benesh in 1967 and which is called 2,3 DiPhosphoGlycerate, or DPG for short. This molecule rests on the symmetry axis between the four sub-units of hemoglobin and can be bound to it or not. For DPG has three negatively charged groups which can be bounded to three particular amino acids in the ß sub-units of a hemoglobin molecule. When that happens, the ß sub-units change their shape and these changes are transferred to the α sub-units attached to them. As a result, the iron atoms are being pushed in a position where it is difficult for O_2 molecules to bind. But the effect is symmetrical. Once an iron atom captures an O_2 molecule, and the chances for that are highest at the lungs, because there oxygen is present in surplus amounts, then its heme group is shifted to a new shape by the effects of the presence of the O_2 molecule. This change of shape is transferred to the α and ß sub-units, causing the three positively charged amino acids at the interface of the ß sub-units to be pushed away from the DPG molecule. The cavity between each of the sub-units is narrowed and the DPG molecule is being extruded. As a result, the iron atoms in the other sub-units are exposed more readily to oxygen, allowing three more O_2 molecules to bind.

The reverse process occurs in the tissues, where the concentrations of CO_2 molecules and H^+ ions are high. These can bind to three particular amino acids in each of the sub-units and when that happens, the shape of the sub-units changes again such that a DPG molecule is able to bind again. As a result, the iron atoms in the heme groups are pushed into a position where their affinity for O_2 molecules is strongly lowered leading to the accelerated release, one by one, of four O_2 molecules.

Since both processes occur in a large number of hemoglobin molecules, the overall result is exactly the Bohr effect: accelerated oxygen-uptake at the lungs and accelerated oxygen-release at the tissues. Incidentally, one needs again the theory of chemical bonding to explain the various interactions between hemoglobin, DPG, O_2 and CO_2 molecules and H^+ ions. Thus, with the help of this theory and the theory of allostery molecular biologists have been able to solve the problem that arose at the level of the physiological programme: how to explain the Bohr effect.

I will later reconstruct the explanation in terms of Kuipers's (1990) reduction steps, but first illustrate my claim that this explanation resulted from the co-operation of holistic and reductionistic research programmes and that these programmes were mutually dependent.

6.3 Reconstruction

6.3.1 Co-operating research programmes

It will be clear that in the reduction of the Bohr effect the *physiological programme* acted as a holistic guide programme. It provided a description of certain (emergent; see below) phenomena at a macro-level, the rate of uptake and release of oxygen by the blood, which it could not explain itself, and thus guided the way to a problem which it could not solve itself. For this solution it depended on the *programme of molecular biology* with the theory of allostery as a hard core. Because this programme succeeded in solving the problem, it acted as a reductionistic supply programme for the physiological guide programme. It was itself dependent on the guide programme, however, for generating the problem.

Actually, however, the example is much more complicated, and hence more interesting,

because it involved at least six research programmes. Apart from the physiological and the molecular programme, these were the biochemical programme, the programmes of x-ray crystallography and electrophoresis, and the programme of structural chemistry with the theory of chemical bonding as a hard core.

The *biochemical programme* played an essential intermediary role by showing that the uptake of oxygen by the blood rests with the binding of O_2 molecules to hemoglobin molecules. This was important information for the physiologists which gave them a better understanding of how oxygen was taken up by the blood. Thus the biochemical programme acted as a supply programme for the physiological programme. At the same time, however, it acted as a guide programme for the molecular programme, because it indicated at which type of molecules molecular biologists should direct their attention. Thus the biochemical programme played a role as an 'interlevel' bridge programme by acting as a guide programme to the physiological programme and as a supply programme to the molecular programme. Thereby, we see that a programme can be at the same a guide programme and a supply programme.

The same applies to the molecular programme. For this programme acted on the one hand as a supply programme for the physiological programme. On the other hand, to be able to play that role it needed the techniques and theories of other programmes and therefore acted as a guide programme for those other programmes. In the first place, it needed the *programmes of x-ray crystallography* and *electrophoresis* to supply the required analysis techniques and the accompanying measuring theories with which the structure of hemoglobin molecules could be unravelled. In the second place, it needed the *programme of structural chemistry* which provided the theory of chemical bonding. With this theory it was not only possible to derive the three-dimensional shape of hemoglobin from the order and properties of the amino acids in the globin-chains, but also to derive the allosteric effects of hemoglobin from its interactions with DPG, O_2, CO_2 and hydrogen ions. Thus both the programmes of x-ray crystallography and of electrophoresis and the programme of structural chemistry acted as supply programmes for the molecular programme. I will return later to the fact that a programme can be at the same time a guide programme and a supply programme.

It is worth mentioning that there is a difference between on the one hand the programmes of x-ray crystallography and electrophoresis and on the other hand the programme of structural chemistry. For the former are examples of *experimental* supply programmes whereas the latter is an example of a *theoretical* supply programme. Theoretical supply programmes provide specific theories with which phenomena at the level of a guide programme can be explained, or, put differently, with which laws or theories at this level can be reduced. Experimental research programmes on the other hand provide measuring techniques and accompanying measuring theories with which the phenomena can be empirically investigated. Thus, they play an essential role in the accomplishment of reductions, but they do not take part in the actual reductions (as logical relations between laws and theories) themselves (Zandvoort 1986a,b).

Thus, we see that in the present example there is a certain stratification of six research programmes and that the relations between these programmes can all be described in terms of the model of co-operating and mutually dependent research programmes. In figure 3 I have pictured these various programmes and the relationships between them.

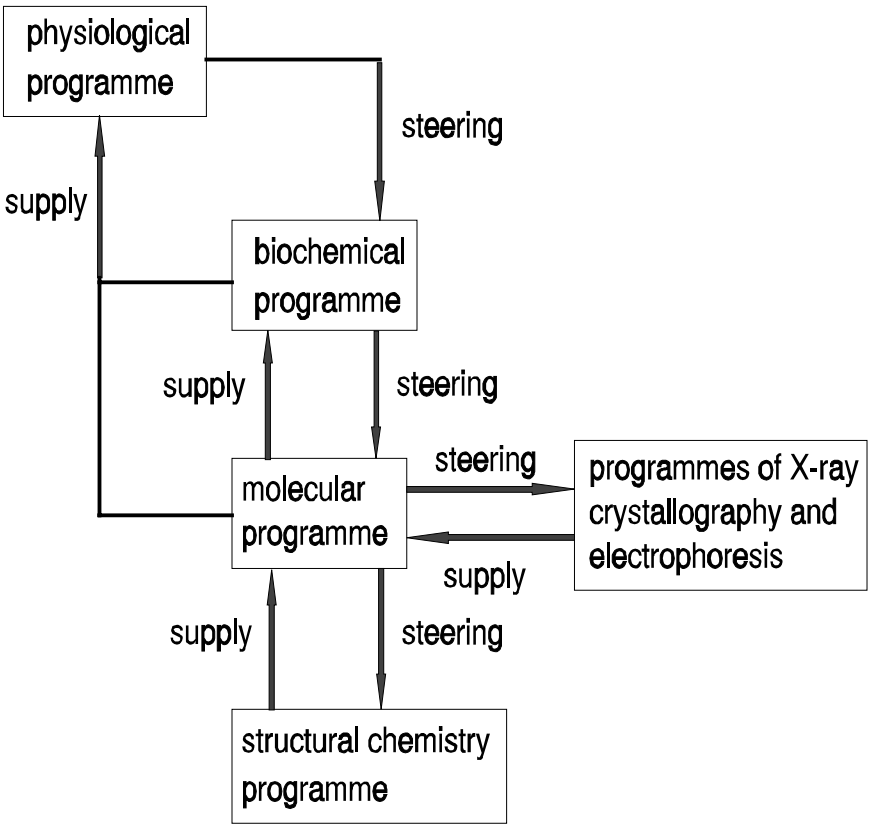

Figure 3: The various research programmes involved in the reduction of the Bohr effect and their mutual relations.

6.3.2 Reduction steps

I will now reconstruct the example in terms of Kuipers's (1990) reduction steps. As in chapter 3 I will discuss the various steps in the reverse order, that is, starting with the application of the (lowest) reducing micro-theory.

The first step can be sketched as an *integrated application and aggregation* step. In this step the theory of chemical bonding is applied to the component parts (amino acids and porphyrin molecules) of a hemoglobin molecule, and the various interactions (bondings) between these parts are aggregated in a complex, non-trivial way. Several auxiliary hypotheses are thereby being used, in particular hypotheses specifying the initial conditions and the boundary conditions of the 'system'. These concern the primary structure of a hemoglobin molecule, that is, the natures (chemical properties) of the amino acids and the order in which they appear in the globin-chains, the nature (chemical properties) of the heme groups (porphyrin molecules), and the molecular milieu in which they occur. By applying the theory of chemical bonding to this system of sub-molecules one can specify precisely which of them will attract and which of them will repel each other and where, as a result, the globin-chains will bend, turn, overlap on themselves and come into contact with each other and with the heme groups. By aggregating all the interactions one can derive from the primary structure the secondary,

tertiary and quaternary structure, respectively, of the whole molecule.

It will be clear that the aggregation step is complicated and non-trivial, because it involves various *types* of interaction between a large number of different *types* of sub-molecules, which have to be 'summed up' in a complex, non-trivial way. Actually this step can be seen as a sequence of individual applications of the theory of chemical bonding followed by an aggregation of these applications. It would go much too far to try and spell out all these applications and the entire aggregation process, because then I would have to specify the chemical properties of approximately four times 140 molecules and then sum up all the atomic and molecular forces and bondings between them. One can imagine the enormous effort it must have taken first to unravel the structure of hemoglobine and next, from the pieces, to derive the shape of the whole molecule.

As it is impossible (and also unnecessary) here to spell out the various amino acids by name and surname, I will formulate the result of this step as the *aggregated regularity* (to be called L1) that if these particular amino acids are being synthesized in this particular order, then, given a certain molecular milieu containing porphyrin molecules, a specific three-dimensional structure appears: a hemoglobin molecule.

The next step is a *transformation* step and more in particular a *correlation* step. In this step the allosteric effects of a hemoglobin molecule are being derived from its interactions with a DPG molecule, O_2 molecules, CO_2 molecules and H^+ ions. For the sake of simplicity I will call one such complex of a hemoglobin molecule, a DPG molecule, O_2 and CO_2 molecules and H^+ ions, a hemoglobin complex. In the present step a correlation hypothesis is being used which actually consists of a causal sketch of the various interactions between the component parts of one such complex. I have already given this sketch in 6.2.3 and will not repeat it here. (Actually this step is equivalent to the application of the theory of allostery to a hemoglobin complex, but I will go into that later, in 6.3.3). The result of this step is a regularity (L2) stating that if the oxygen pressure is high and the acidity is low (that is, high pH), then the binding of one O_2 molecule to one of the iron atoms in a hemoglobin molecule leads to the accelerated binding of three more O_2 molecules to the molecule, and that if the oxygen pressure is low and the acidity is high (low pH), then the binding of CO_2 molecules and H^+ ions to a hemoglobin molecule leads to the accelerated release of four O_2 molecules. This regularity concerns only one hemoglobin complex and therefore, in view of the following step, can be called an *individual regularity*.

For the next step is again an aggregation step. In this step the allosteric effects of a large number of hemoglobin molecules are being aggregated. Contrary to the first aggregation step, the present one consists of a simple addition. The result is the *aggregated regularity* (L3) that at high oxygen pressure and low acidity the binding of O_2 molecules to hemoglobin molecules leads to the accelerated binding of more O_2 molecules to hemoglobin molecules, and that at low oxygen pressure and high acidity the binding of CO_2 molecules and H^+ ions to hemoglobin molecules leads to the accelerated release of O_2 molecules by hemoglobin molecules.

The final step is again a transformation step, but now in particular an *identification* step. In this step the information provided by the biochemical programme is being used that the uptake of oxygen by the blood rests with the binding of O_2 molecules to (iron atoms in) hemoglobin molecules. This information acts as a bridge principle in the form of an *identification hypothesis* ('ontological identity relation'). However, as has become clear in chapter 4, we have to be very careful in formulating identification hypotheses. In the present

case there are two possibilities of formulating the relation, namely as a thing-identity (the first obvious possibility) or as an attribute-identity. As a thing-identity the relation would be that the binding and release of O_2 molecules by hemoglobin molecules is identical to the uptake and release of oxygen by the blood. However, this seems to me incorrect, since the uptake and release of oxygen by the blood involves much more that just the binding and release of O_2 molecules by hemoglobin molecules. It involves the breathing in of air (containing oxygen) by the mouth or nose and the lungs, diffusion of oxygen to the blood vessels, absorption by the red blood cells and then the binding of O_2 molecules by hemoglobin molecules; and next the transport (by means of, among other things, the beating of the heart) of the blood to the tissues, where, as far as oxygen binding is concerned, roughly the reverse process occurs in the capillaries. Thus, the most we could say is that the uptake and release of oxygen by the blood is partially identical to the binding and release of O_2 molecules by hemoglobin molecules. But I think the identity is better formulated as an attribute-identity. For after all the Bohr effect is not so much concerned with the uptake and release of oxygen by the blood as with the *rates* at which this occurs. Formulated as an attribute-identity the relation then states that the rate at which O_2 molecules are being bounded and released by hemoglobin molecules is exactly the same as (identical to) the rate at which oxygen is taken up and released, respectively, by the blood. With the help of this bridge principle the following regularity (L4) can now be derived: at high oxygen pressure and low acidity oxygen is taken up more quickly by the blood and at low oxygen pressure and high acidity oxygen is released more quickly by the blood. L4 is the Bohr effect.

6.3.3 Application or correlation?

As already mentioned, the above correlation step can also be seen as the result of the application of the theory of allostery to a hemoglobin complex. We can draw two interesting conclusions from this.

Firstly, it means that actually with the first two reduction steps (integrated application and aggregation, and correlation) the theory of allostery, applied to a hemoglobin complex, has been reduced to the theory of chemical bonding. And this in turn means that the reduction of the Bohr effect does not consist of one heterogeneous micro-reduction but is actually composed of two such reductions: (1) the reduction of the Bohr effect to the theory of allostery (through application, aggregation and identification) and (2) the reduction of the theory of allostery, applied to hemoglobin, to the theory of chemical bonding (through integrated application and aggregation, and correlation).

The second conclusion is more intriguing and leads to some complexities and relativisms. This conclusion is that, apparently, a certain step in a reduction can be seen as on the one hand an application step and on the other hand a correlation step. For the step which, starting from the theory of chemical bonding, must be called a correlation step (the causal sketch of the interactions between the component parts of a hemoglobin complex) must be called an application step when starting from the theory of allostery. This application step leads to exactly the same causal sketch, and hence the same result, as the correlation step starting from the theory of chemical bonding.

Whether we call this step a correlation step or an application step depends on the level of organization which we take as a starting point for the reduction. When we start from the primary structure of hemoglobin, the theory of chemical bonding is the (lowest) reducing

micro-theory and the theory of allostery then acts as a correlative auxiliary hypothesis connecting the theory of chemical bonding with the Bohr effect. However, when we take as a starting point (initial condition) not the primary structure of hemoglobin but a hemoglobin complex, then the step first described as a correlation step now becomes an application step, consisting of the application of the theory of allostery to this complex. And then the theory of allostery would not act as a correlative hypothesis but as the (then lowest) reducing micro-theory. And it is a reducing micro-theory, for what we would get then is simply the first of the two above-mentioned heterogeneous micro-reductions.

The same phenomenon can be seen at the level of the application of the theory of chemical bonding to the primary structure of hemoglobin. I have referred to the first reduction step as an integrated application and aggregation step and, when starting from this primary structure, this seems to me a correct qualification. As I said before, this step can be seen as a sequence of individual applications of the theory of chemical bonding (to different types of interactions between different types of sub-molecules) followed by the aggregation of the results of these applications. However, the step might just as well be called a correlation step. For after all, it relates to *interactions* between the component parts of a hemoglobin molecule and it actually consists of a same sort of causal sketch as that of the interactions between the component parts of a hemoglobin complex. However, we can call this step a correlation step only when we would take another starting point for the reduction. For when we wouldn't take as a starting point the primary structure of hemoglobin but, say, the point at which the synthesis of the separate amino acids begins, as determined by the genetic code for the production (synthesis) of hemoglobin, then it would not be the theory of chemical bonding playing the role of (lowest) reducing theory, but molecular genetics. And the causal sketch of the forming of the quaternary structure of hemoglobin out of, consecutively, its primary, secondary and tertiary structure, which can be given on the basis of the theory of chemical bonding, would then play the role of a correlation hypothesis. Thus, when starting from the primary structure of hemoglobin, this step may be called an (integrated) application (and aggregation) step, but when starting from a lower level it may be called a correlation step.

The point is, of course, that both the theory of allostery and the theory of chemical bonding are *inherently causal* theories that have *interactions* between molecules as their *domain*. Applications of such theories to their own domain (or level of organization) lead to inherently causal sketches (c.q. explanations) which, however, given the fact that they are applications, cannot be called correlation steps. However, when viewed from a lower level of organization, and starting from a 'lower' reducing micro-theory, they can be called correlation steps. This reasoning, if correct, indicates that a certain theory can play the role of both a reducing micro-theory and a correlation hypothesis and that the qualification of a theory as either a reducing micro-theory or a correlation hypothesis depends on the level of organization relative to which it is considered. I will return to this point later, because it is related to another point, namely the relativity of the terms 'holistic' and 'reductionistic' when applied to theories or research programmes (see 6.4.2).

6.3.4 Emergence

After all that I have said about emergence in chapter 5, it should come as no surprise that the present example deals with emergent properties or phenomena. Yet the interesting question is at which level(s) of organization emergence occurs.

In chapter 5 I have argued that we can talk of emergence at the level of the whole iff a micro-reduction takes place with the help of either non-trivial aggregation (and identification) and/or correlation. On these grounds we can establish that in the present example emergence occurs at both the level of (the quaternary structure of) hemoglobin molecules with respect to their component parts (porphyrin molecules and globin molecules, or *their* component parts) and the level of the Bohr effect (blood) with respect to the level of hemoglobin molecules. For in order to arrive at the structure of hemoglobin as a whole from the properties of its component parts we need non-trivial aggregation of interactions between these parts (or correlation). And in order to arrive at the specific oxygen-binding properties of the blood (the Bohr effect) from the properties of hemoglobin molecules we need, besides trivial aggregation and identification, correlation (interactions with DPG etcetera). In the first case the non-trivial aggregation step guarantees that we can talk of emergence at the level of the whole, in the second case the correlation step does so.

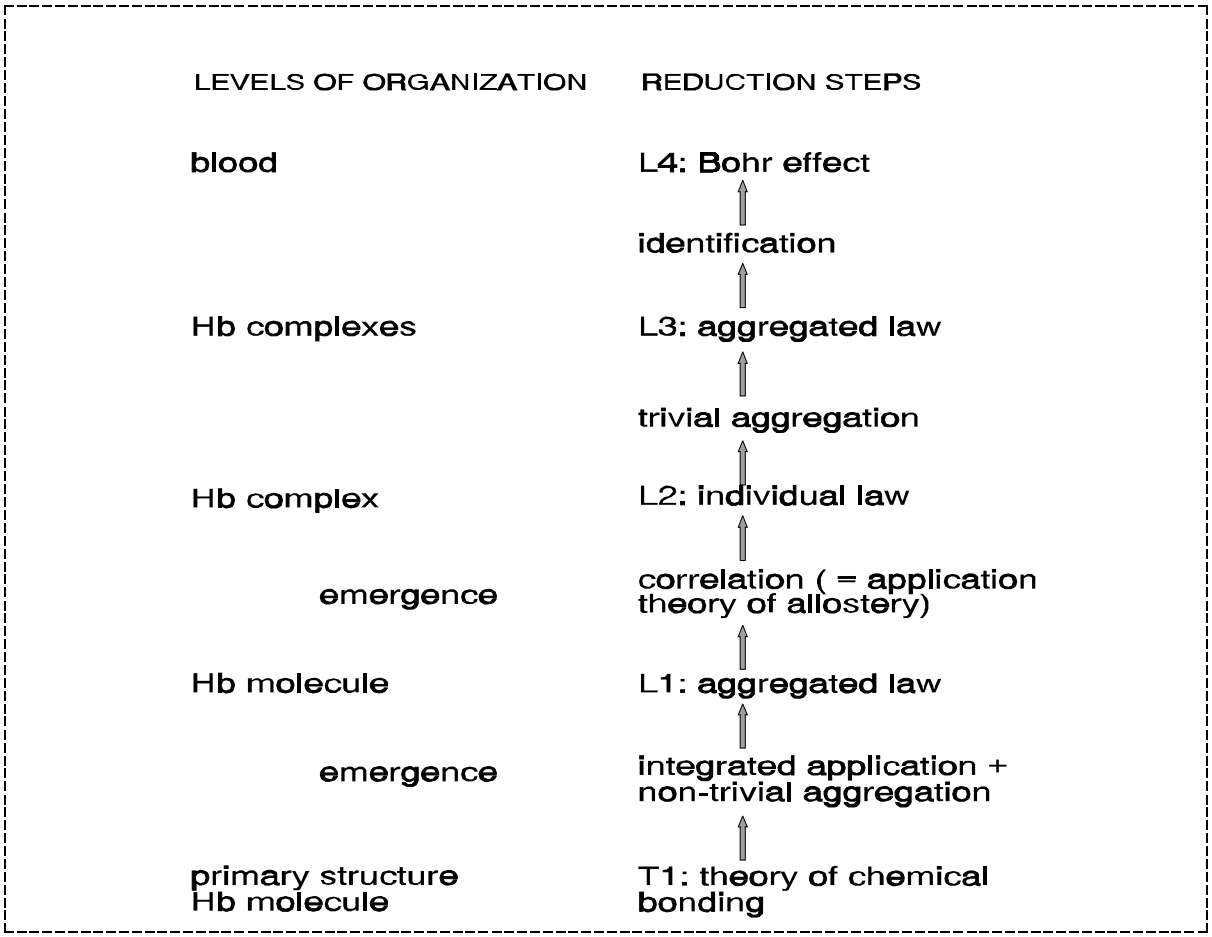

Figure 4: Reduction steps and levels of organization involved in the reduction of the Bohr effect.

I have summarized the various reduction steps and the levels of organization they relate in figure 4.

6.4 Concluding remarks

6.4.1 Reduction: construction or reconstruction?

The reduction of the Bohr effect is a nice example of heterogeneous micro-reduction of a macro-law about emergent biological phenomena, and it is also a nice example of the mutual dependence of holistic and reductionistic research programmes. The first conclusion we can draw from the example is therefore that neither an exclusively holistic nor an exclusively reductionistic research strategy is sufficient for the clarification and understanding of phenomena at a certain level of organization and, hence, more generally, for the growth of knowledge. Both strategies are separately insufficient and jointly necessary. The best global strategy seems to be, therefore, a mixed strategy where holistic research of higher levels is supplemented or alternated by reductionistic research of lower levels, depending upon the state of the art and the developmental stages of the respective disciplines.

It can be seriously questioned, however, whether macro-laws or theories in biology, such as the Bohr effect, could ever be derived from (reduced to) micro-theories *if the former were not discovered or developed first*! In other words, it can be seriously questioned whether macro-laws or theories could ever be *constructed* on the basis of micro-theories. This is the more unlikely, since it would require the formulation of bridge principles connecting terms in a micro-theory with terms in an as yet *unknown* macro-law or theory! Suppose that we would know nothing at all about the uptake and release of oxygen by the blood. Would we then ever be able to derive something like the Bohr effect from the theory of chemical bonding alone, or even from the theory of allostery alone? Would the theory of allostery have ever been developed had there not first been recordings of the specific catalytic effects of enzymes and other proteins? This seems to me highly unlikely. Although the possibility of reductions as constructions cannot and should not be ruled out completely (and there appear indeed to be examples, such as Dalton's prediction of the law of multiple proportions)[40], it seems more likely to me that reductions like the one discussed here will generally be *reconstructions*, that is, explanations-after-the-fact of first discovered or developed macro-laws or theories.

If this is correct, it would mean that the most plausible course of things, the most general pattern of development, is that one starts with holistic research at the level of some whole, resulting in macro-laws or theories about this whole, followed by reductionistic research at the level of the component parts, and interactions between them, leading to micro-theories and bridge principles with which the macro-laws or theories can be explained. This would once more illustrate my thesis that reductionistic (supply) programmes are dependent upon the fruits of holistic (guide) programmes (and vice versa).

It is interesting, and illuminating, in this respect to return once more to the formulation of the doctrine of emergence by Mayr (1982), that is, to the claim that "the characteristic behaviour of the whole could not, even in theory, be *deduced* from the most complete knowledge of the parts" (see 5.2.1). I have agreed with Nagel (1982) that the empirical

[40]This example was pointed out to me by Theo Kuipers. He also pointed out, however, that the 'holistic' laws of Lavoisier and Proust were discovered first, and that after the successful reduction of those laws by Dalton's theory, no *new terms* were needed to predict the law of multiple proportions.

component of the doctrine (the theory of emergent evolution or its 'contemporary' counterpart) should be distinguished from the epistemological claim about the unpredictability (or irreducibility) of 'emergent' properties at higher levels of organization. We can now conclude that emergentists may be right in the sense that it is unlikely that higher-level properties or phenomena can be *predicted* (or 'construed') on the basis of micro-theories alone. However, prediction or construction is something different from reduction in the sense of reconstruction (explanation-after-the-fact).

6.4.2 'Holism' and 'reductionism'

I have noted in section 6.3.3 that the qualification of a (causal) theory as either a reducing micro-theory or a correlation hypothesis depends on the level of organization relative to which it is considered. The theories of chemical bonding and of allostery are inherently causal theories which, when applied at their own level of organization (or domain), can play the role of reducing micro-theories, but also, when viewed from a lower level, the role of correlation hypotheses.

This point is related to another conclusion we can draw from the example, namely that the terms 'holistic' and 'reductionistic', when applied to theories or research programmes, are also extremely relative in the sense that they too should always be related to a certain given level of organization. For instance, molecular biology counts as *the* paradigm of reductionistic research programmes in biology, but this is true only if the programme is related to higher-level programmes such as physiology. At the same time, it can be characterized as 'holistic' when related to lower-level programmes such as physical chemistry. In the present example, the molecular programme acted on the one hand as a reductive ('reductionistic') supply programme for the physiological programme, but on the other hand as a 'holistic' guide programme for the programme of structural chemistry. The theory of allostery acted on the one hand as a reducing micro-theory with respect to the Bohr effect, but on the other hand as a 'holistic' correlation hypothesis connecting the theory of chemical bonding with the Bohr effect.

Maull (1977) and Darden and Maull (1977; see also Bechtel 1986, 1988, 1993) have argued that there is an important role in science for complex, so-called 'interfield' or 'interlevel' theories which relate 'fields', disciplines or levels with one another without, however, reductions taking place. They mention the theory of allostery in particular as such an 'interfield' theory connecting biochemistry with physical chemistry. In their view this does lead to unity of science, but thus without reductions. The present example makes clear, however, that the qualification 'without reductions' can be left out. The theory of allostery can indeed be seen as a 'holistic' interfield or interlevel theory, connecting biochemistry with physical chemistry, but on the other hand it is a causal, reducing theory with respect to enzyme kinetics in physiology. Moreover, in its specific application to hemoglobin, the theory itself has been proved to be reducible to the theory of chemical bonding. Thus, there need be no conflict between the notion of interfield or interlevel theories and the reduction thesis (see also Schaffner 1993a, who is also sympathetic towards the notion of interfield theories, but who has incorporated them in his general reduction model).

What was said of molecular biology applies also to biochemistry. Biochemistry, too, is generally seen as reductionistic, which indeed it is when related to, for example, physiology. However, in the reduction of the Bohr effect the biochemical programme also played the role

of a 'holistic' guide programme for the molecular programme (and the programmes of x-ray crystallography and electrophoresis) and certainly for the programme of structural chemistry.

The same applies also to physiology. For physiology is generally considered to be 'holistic' with respect to molecular biology, not to mention molecular genetics or physical chemistry. At the same time, however, it counts as 'reductionistic' with respect to, for example, ethology or behavioral ecology. In the same way and more in particular neurophysiology counts as 'reductionistic' with respect to psychology, but is 'holistic' when related to, say, physical chemistry.

In short, whether a theory or programme is to be characterized as 'holistic' or 'reductionistic' depends primarily on the level of organization relative to which it is considered. A theory or programme can be 'holistic' with respect to a lower level but at the same time 'reductionistic' with respect to a higher level.

6.4.3 Partial reduction

As noted in the preceding chapter (section 5.5.3), most reductions are partial and not complete. Of course, this does not apply to reductions of laws, but to reductions of theories. Reductions of theories are almost always partial, either in the sense that only part of a theory can be derived from another theory plus auxiliary hypotheses (Popper 1974b; Bunge 1977), or in the sense that only part of the domain of a theory is reduced (Zandvoort 1986b). The latter is also the case with the reduction of the theory of allostery. For as we have seen it is not the theory of allostery that has been reduced to the theory of chemical bonding, but only its specific application to hemoglobin molecules. The domain of the theory is much larger than just hemoglobin molecules, however, and includes all allosteric enzymes and other proteins. Though the reduction of its application to hemoglobin is not the only example, and it may even be that at present the majority of its applications has been reduced, still the number of successful reductions of the theory's applications is smaller than the total number of applications. In other words, the successfully reduced domain of the theory is still smaller that its in principle reducible domain. Now nothing appears to stand in the way of the further reduction of this in principle reducible domain except the troublesome and time-consuming analyses of the respective proteins that have to be performed. However, as long as these analyses have not been completed we can only speak of a partial reduction of the theory.

Of course this is not an argument against reductionism, but it does mean that as long as the in principle reducible domain of a macro-theory is larger than its successfully reduced domain, we can only turn to this theory itself for concrete insights into its as yet to be reduced domain, that is, to the 'holistic' theory or to the 'holistic' programme that has this theory as its hard core. And this in turn means that as long as this programme is still in active development, it will always, or at least for a long time, stay a few steps ahead of the reducing programme. A possible fear on the part of holists, that they loose their research area by the activities of reductionistic programmes, seems therefore largely ungrounded. Moreover, even when a macro-theory is reduced completely, it it still much more convenient to work with this theory than with the reducing micro-theory: it is much more convenient to talk about allosteric proteins, or about allosteric properties of proteins, than to use the equivalent terms of structural chemistry (see also Zandvoort 1986b).

6.4.4 The function of hemoglobin

To conclude this chapter it should be noticed that the reduction of the theory of allostery, and thereby also the reduction of the Bohr effect, is incomplete in yet another respect. This concerns the nine amino acids per globin molecule which appear to be principally responsible for the ultimate three-dimensional structure of hemoglobin (see 6.2.2). As mentioned, the hemoglobin molecules of different animal species differ in most of the approximately 140 amino acids per globin-chain, but nine of them are identical in all species, that is, rest on the same positions in the globin-chains. The reduction is incomplete because it leaves unexplained why just these nine amino acids have been 'conserved' and why not more or less, or why not others. That is not to say that there is no explanation for this. There is. But this explanation states that exactly these nine amino acids are principally responsible for the ultimate shape of hemoglobin molecules and hence for their allosteric effects and hence for their *function*. However, this is not a causal, reductive explanation in terms of the theory of chemical bonding, but a *functional explanation* in terms of the contribution of these amino acids to the structure of hemoglobin molecules as a whole (and hence to the role of these molecules in oxygen transport by the blood).

This applies in general to the macro-molecular structures investigated by molecular biologists. For the time being molecular biologists are forced to take the specific compositions of these molecules, their primary structure, as given, to accept them as initial conditions. Most of these molecules can presently be described completely in chemical terms, and chemical laws and theories can be applied to them, such as in the case of hemoglobin molecules. But the reason for their specific composition can as yet not be given without reference to their function in the larger biological whole (see also Schaffner 1969a; Rosenberg 1985, chapter 4).

Because functional explanations are extremely controversial and are used by holists as an argument in favour of the autonomy of biology, whereas reductionists maintain that they are to be replaced by 'standard' causal explanations, the next chapter will be devoted entirely to the role and status of functional explanations in biology.