

The problem of biological hierarchy

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The central purpose of these discussions, which grew out of the meetings at Villa Serbelloni during the last three years, has been to explore the significance of theory in biology – ‘theory’ in the sense of general principles characteristic of the living states of matter. Since I was trained as a physicist, my first two contributions to these discussions were attempts to define the problem of reducing molecular hereditary processes to elementary physical laws. I realized that many molecular biologists had already claimed to have accomplished this. But what they have developed is a model of the cell which behaves very much like a classical machine or automaton in which the ‘secret of heredity’ is asserted to be found in the ‘normal’ chemistry of nucleic acids and enzymes. Except for the fact that these machine parts are single molecules, the implication is that parts functioning like a machine can be described as a machine, and machines are understood in terms of elementary physical laws [1].

Now while there is no doubt that the machine is an appealing analogy, and that machine language is useful for describing some aspects of living matter, this language evades the two essential mysteries of life that are evident from the physicist’s point of view. In the first place, if you ask what is the ‘secret’ of a computing machine, no physicist would consider it any answer to tell you what everyone already knows – that the computer obeys all the laws of mechanics and electricity. If there is any secret, it is in the *unlikely constraints* which harness these laws to perform highly specific and reliable functions. Similarly, if you ask what is the secret of life, you will not impress most physicists by telling them what they already believe – that all the molecules in a cell obey all the laws of physics and chemistry. The real mystery, as in any machine, is in the origin of the highly unlikely and somewhat arbitrary constraints which harness these laws to perform specific and reliable functions. This is the problem of hierarchical control which I shall discuss in this paper.

The second mystery is how one actually describes the existing machine-like constraints in single molecules. It is one thing to believe that all molecules obey the laws of quantum mechanics on philosophical principles, and quite another thing to actually apply these laws of motion to molecules that perform such intricate, rapid, and reliable operations as do enzyme and substrate. In my first

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paper [2], I pointed out that these molecular machines present, for the physicist, some profound problems, which go beyond the classical machine language used in most molecular biological models. In all hereditary machines, or machines which execute logical operations, the constraints must be non-integrable (non-holonomic). Such constraints can be appended easily to the classical dynamics, but they present formal and conceptual difficulties in the language of quantum mechanics. I indicated also why the allosteric enzyme must operate as a non-integrable constraint in order to execute hereditary operations. Furthermore, I emphasized that hereditary machines must rely on statistical correlations and must consequently be subject to fluctuation errors. These errors normally increase with small size and high rates of operation. Therefore, any claim that life has been reduced to physics must at least be supported by an account of the dynamics, statistics, and operating *reliability* of enzymes in terms of quantum mechanical concepts. Finally I proposed that the exceptional speed and reliability of enzymes was not simply a useful property, but the essential requirement for life. It has been a recurring conjecture among physicists that only quantum mechanical properties can distinguish this reliable behavior of life from the behavior of classical machines with which life is, we believe, incorrectly compared [3].

I had hoped that by the second Bellagio meeting I might be able to suggest how logical properties or codes of molecular dimensions in cells could be approached using quantum mechanical formalism. But this problem is closely related to the measurement problem in quantum mechanics, which requires associating the quantum concepts of a state with the idea of a classical observable. This means using both a dynamical and statistical description of the same system. As I looked deeper into this problem, I began to appreciate what many physicists and mathematicians had realized long ago, that this is not only a formal problem, but one which also involves the informal meanings of *theory* and *measurement* and their relationship [4]. Consequently, my second Bellagio paper [5] was only a restatement of the questions which living systems generate for the physicist if he tries to perform a serious reduction to the quantum laws of motion.

By the time of the third Bellagio meeting, I had made little direct progress on this reduction problem. Instead, I returned to the origin of life problem and the mystery of how the unlikely constraints of transfer enzymes or biological codes could have come into existence spontaneously. Here the question is not, *how does it work*, but rather, *how did it arise*. Without giving it much thought, I had hoped that these two questions – how an enzyme can be described as a quantum mechanical system, and how a protoenzyme might arise some five billion years

ago in a sterile sea – could be studied separately. But again I began to appreciate what many biologists had realized long ago, that the more we learn about the detailed relations of biological structure to its function, the more difficult becomes the problem of how these relations between structure and function arose.

Recent approaches to molecular biology tend to produce over-emphasis on the idea that if we understand the details of cellular events, then we are more likely to understand the origin and significance of these events. This has proven to be a half-truth. We certainly need to know the mechanism, but the more details we learn, the less reasonable appears any theory of the origin of the organization which integrates these mechanisms. Function is never determined by a particular structure itself, but only by the context of the organization and the environment in which this structure is embedded. Nor is structure determined by function alone, since many different structures can perform the same function. Similarly a measuring device is never determined by its particular structure but only by its interaction with the physical system being measured. And again the structure of the measuring device is not determined only by what is to be measured, since there are many possible devices which will perform this measurement function. In very much the same sense that physical theory, however complete, does not encompass measurement, the knowledge of biological structure, however complete, does not encompass its function [6].

► *What is the central problem?* In approaching this long-standing structure-function question, I think it is becoming clear that we get nowhere by separating the reduction-type question, *how does it work*, from the origin-type question, *how did it arise*. These are really two ways of viewing the same basic problem. I shall call this the problem of the description of hierarchical interfaces. A hierarchy in common language is an organization of individuals with levels of authority – usually with each level subordinate to the next higher level and ruling over the next lower level. However, neither the authority nor the subordination between levels is complete. Each level has its own laws or rules which control the behavior within each level. The effect of the subordination of the lower level to the hierarchical rule is to constrain or integrate the activities of the individuals so that they function coherently.

If there is to be any theory of general biology, it must explain the origin and operation (including the reliability and persistence) of the hierarchical constraints which harness matter to perform coherent functions. This is not just the problem of why certain amino acids are strung together to catalyze a specific reaction. The problem is universal and characteristic of all living matter. It occurs

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at every level of biological organization, from the molecule to the brain. It is the central problem of the origin of life, when aggregations of matter obeying only elementary physical laws first began to constrain individual molecules to a functional, collective behavior. It is the central problem of development where collections of cells control the growth or genetic expression of individual cells. It is the central problem of biological evolution in which groups of cells form larger and larger organizations by generating hierarchical constraints on sub-groups. It is the central problem of the brain where there appears to be an unlimited possibility for new hierarchical levels of description. These are all problems of hierarchical organization. Theoretical biology must face this problem as fundamental, since hierarchical control is the essential and distinguishing characteristic of life.

► *The failure of fact-collecting answers.* The strongest criticism of theoretical biology is that new facts often make theory appear irrelevant. This is a valid criticism for narrow theories which try to guess *how things work* at one level, since that question is answered on any one level by simply looking in more and more detail at what is actually happening. But a theory of general biology is not simply a set of descriptions of each level. It must be a theory of the levels themselves. Of course we must know also the detailed facts at each level, but I have very little confidence that only by collecting more facts we shall ever explain the hierarchical interfaces which created these levels in the first place.

Of course it is true also that much of the progress in both physical and biological sciences has come from choosing to concentrate on one level of organization at a time. Within the bounds of each level, languages grow in precision and formality; but, paradoxically, they tend to become incompatible with the languages at neighboring levels. For example, in physics, particle mechanics and thermodynamics were developed independently to describe different levels of complexity. Statistical mechanics was at first an attempt to bridge the gap between descriptions of very small and very large numbers of particles. And yet, to the extent that dynamical and statistical formalisms grew more precise, the gap was not bridged, but became even more impassable, since the statistical concept requires a 'postulate of ignorance' about the dynamical variables which is incompatible with the complete dynamical description. I believe that very similar difficulties will arise at all hierarchical interfaces in biological systems. For example, the more detailed becomes our machine description of coding or information-transfer enzymes, the more difficult, and perhaps incompatible, will be the formal quantum mechanical description of the same systems. In a similar

way, the more abstractly we define the logical operations of the brain which we associate with formal thought processes, the more difficult it becomes to imagine an exact physical representation of these processes. In all these cases, we manage to gain formal precision at the higher level of description only by sacrificing some of the details of the motions at the lower levels.

The root of this problem is clearly not in the detailed facts of one level or another, but in the relations between levels. Therefore in order to better understand the origin and nature of hierarchical organization, I shall not direct your attention to the detailed descriptions of each level, but rather to the division between levels which I call the hierarchical interface.

► *The failure of one-sided answers.* In order to see the central problem of hierarchical organization more clearly, it is helpful to look at the difficulties which arise when the hierarchic interface is viewed from only one side or the other. Viewed from the lower side of this interface, the elementary laws are regarded as the given conditions and the problem is to see how the hierarchical constraints arise to perform integrated function at the higher level. Viewed from the upper side of this interface, the hierarchical constraints are regarded as the given conditions and the problem is to see if the integrated function is consistent with the elementary laws.

Two examples of these views may be found in recent writings of Francis Crick and Michael Polanyi. Crick [7] in his book *Of Molecules and Men* defends complete reductionism in biology because, by assuming all the hierarchical structure of cells as given, he feels that all the resulting elementary motions can be explained in terms of ordinary physics and chemistry. At the other extreme is a paper by Polanyi [8] on *Life's Irreducible Structure*, in which he assumes that all the molecules obey physical laws but claims that the origin of the constraints or boundary conditions which result in hierarchical integration are irreducible to those laws. There are, of course, many advocates on both sides of the question, but these two writings, read side by side, form a remarkable example of forceful arguments ending up with opposite conclusions. But of course the reason is that Crick and Polanyi had no common ground in the first place. They began on opposite sides of a hierarchical interface.

Crick makes it clear at once that he is only talking about *how it works* not *how it got that way*. He is satisfied that ordinary physics and chemistry tell us how it works and that the theory of evolution is the obvious answer to how life got that way; but he doubts that the process of evolution is predictable. Then he goes on to say that this distinction between how it works and how it evolved

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is what is confusing Elsasser and Polanyi in their approach to biology. From this point of view the hierarchy problem does appear more as a source of confusion rather than the central issue in biology.

Polanyi, on the other hand, points out that it is not the ordinary laws of physics and chemistry which are significant for understanding the nature of life, but rather the exceptional boundary conditions through which cells harness the laws to perform new behavior. He believes that the evolution of hierarchical control at higher and higher levels is the essential characteristic of life, but he asserts that although higher levels are dependent on the laws of lower levels, they are not reducible to them. Polanyi clearly sees the hierarchy problem as central to biology, but judges it irreducible.

To some extent it was my disagreement with molecular biologists' assertions that life was already essentially reduced to physics that led me in my previous Bellagio papers to discuss the nature of molecular hereditary processes in more elementary physical language [2, 5]. While I remain hopeful that the question, *how it works*, can eventually be described in terms of elementary physics, I do not think Crick or any other molecular biologist has given any evidence that this has been done. The experimental results of molecular biologists are impressive, but to a physicist their claims usually sound badly overstated. One misunderstanding is caused by different 'ground rules' for what is acceptable as an explanation or reduction of life to physics. Crick, along with many biochemists, tends to equate 'reduction' with duplicating certain cellular reactions in a test tube, as if 'vital principles' or 'unclear thoughts' abhor test tubes. There is also the tacit assumption that if a chemist can synthesize an active enzyme by stringing together the right sequence of amino acids, then enzyme behavior must present no 'real difficulty'. But is not the 'real difficulty' to determine the 'right sequence'? Even Crick admits that, 'We could only synthesize a good enzyme, at this stage in our knowledge, by precisely imitating what nature has produced over the course of evolution rather than designing one ourselves from first principles.' Again, with regard to replicating nucleic acids, he says, 'There is nothing, therefore, in the basic copying process, as far as we can see, which is different from our experience of physics and chemistry except, of course, that it is exceptionally well designed and rather more complicated.' But it seems to me that it is precisely this exception and only this exception which distinguishes living from non-living matter! Therefore it is this 'exceptional design' which must be reduced to physics. 'Exceptional design' at any level is what creates the new hierarchical function.

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To get around this problem, Crick, along with most molecular biologists, invokes a non-physical theory – the theory of evolution. They simply assert that evolution by natural selection can account for whatever ‘design’ and ‘complication’ the cell (and the biochemist) needs to make things work. There are at least three difficulties with this assumption. In the first place, there is no evidence that hereditary evolution occurs except in cells which already have the complete complement of hierarchical constraints, the DNA, the replicating and translating enzymes, and all the control systems and structures necessary to reproduce themselves. The theory of evolution presently is a theory which applies only to pre-existing, highly evolved, hierarchical organizations. Secondly, the theory of evolution does not account for the origin of new hierarchical levels from aggregations of lower level components. This could be disputed on the grounds that ‘accounting for’ means to explain but not to predict, and that hierarchies can be ‘explained’ as systems with greater ‘fitness’ than subsystems which do not have the integrated behavior produced by the hierarchical control. If such arguments are not circular, at least they beg the question. Living matter is distinguished from non-living matter in the final analysis, not because of its molecular structures, but because it evolves quite differently from non-living matter. Living matter exists only because it evolves in time in a course which laws of motion have not yet suggested. It is not a question of predicting details, which indeed may be impossible. But to claim reduction of life to physics we must have at least some hint that any functional hierarchical constraint can arise from the laws of a lower level. Theoretical biology should try to provide this hint.

Crick concludes by admitting that the origin of life and the nature of consciousness may be ‘difficult areas’; but by looking only at *how it works*, which means accepting the hierarchical complexities of biological organizations as they presently exist, and excluding the problems of hierarchical origins, Crick tries to convince us that physics and chemistry explain everything.

Polanyi, of course, assumes that all molecules work according to natural laws, but since no one has accounted for hierarchical organizations by these laws, he claims there must be principles of organization which are not reducible to the laws of physics and chemistry. Evolution to Polanyi is ‘. . . a progressive intensification of the higher principles of life’. These principles, he says, depend for their expression on the laws of lower levels, but each higher level has a context of meaning which is unpredictable from the lower levels. Thus by looking only at the highly evolved boundary conditions and excluding detailed attempts to describe how even simple boundary conditions could arise, Polanyi tries to convince us

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that the origin of hierarchical boundary conditions can never be explained by elementary laws of motion.

I use Crick's and Polanyi's papers as examples, not to make a philosophical plea for either reductionism or vitalism but, as I said, to illustrate how a hierarchical interface tends to raise two types of question. Viewed from the upper level of the hierarchy the existing constraints are generally taken for granted and the significant question seems to be, *how does it work*. The answer found from this perspective usually amounts to the discovery that the parts obey the laws of the lower level. To this extent there is reduction. On the other hand, viewed from the lower level of the hierarchy it is the laws of motion which are generally taken for granted and now the significant question seems to be, *how could the constraints arise*. The answer usually given from this perspective amounts to the conclusion that the constraints are not derivable from the laws of the lower level. To this extent reduction appears impossible.

If anyone takes care to formulate both of these questions with precision, then I think he will find that both answers are correct for their respective questions. Nevertheless, either of these answers alone has tended, for hundreds of years, to stimulate great disputes. Since the two questions arise from disjoint perspectives, the arguments are often largely polemical. Of course I do not desire or expect to avoid arguments over this discussion. All I can say is that I am not at all satisfied with either the claim that physics explains how life works or the claim that physics cannot explain how life arose.

► *The concept of hierarchy*. To begin I shall limit my use of the idea of hierarchy to *autonomous* hierarchies. That is, to collections of elements which are responsible for producing their own rules, as contrasted with collections which are designed by an external authority to have hierarchical behavior. I want to talk only about what might be called natural hierarchies rather than artificial or supernatural hierarchies, such as man-made machines or 'special creations' of any kind. Secondly, I shall assume that all my examples are a part of the physical world and that *all the elements obey the normal laws of physics*. This does not mean that I assume a reductionist attitude. The question of what reduction can mean will become clearer, I believe, only after we discover the necessary physical conditions for a hierarchical interface. Thirdly, I shall limit my definition of hierarchical control to those rules or *constraints* which arise within a *collection* of elements, but which affect *individual* elements of the collection. This is the normal biological case where, for example, in society a set of laws is enacted by the collective action of the group but applied to individuals of the group; or in

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the development of the organism, the collective interactions of neighboring cells control the growth or genetic expression of an individual cell; or in the enzyme where collective interactions of many bonds control the reaction of an individual bond.

Finally we must recognize the essential characteristic of hierarchical organization, that the collective constraints which affect the individual elements always appear to produce some *integrated function* of the collection. In other words, out of the innumerable collective interactions of subunits which constrain the motions of individual subunits, we recognize only those in which we see some coherent activity. In common language we would say that hierarchical constraints produce specific actions or are designed for some purpose.

Right here I shall stop my description rather abruptly, since in talking about 'function' I have passed over the hierarchical interface which always causes so much argument. Let me return instead to the first three conditions for a hierarchy (1) autonomy, that is, a closed physical system, (2) elements in the system which obey laws of physics, and (3) collections of elements which constrain individual elements. I want first to express these conditions in the language of mechanics so that we can see the implications of these conditions as simply as possible.

► *Structural hierarchies.* Descriptions of nature using the language of physics usually satisfy our first condition of autonomy by assuming a closed system. In classical mechanics the elements or particles in this system are said to have a certain number of degrees of freedom, which is just the number of variables necessary to describe or predict what is going on. Our second condition is that the particles of the system follow the laws of motion. Classically this means that, given their initial positions and velocities at a given time, and with arbitrarily high precision, the trajectories of the particles can be predicted in the future or explained in the past. But if we are restricted to classical physics there is no way in which the third condition can be given much significance, because it requires a 'collection' of particles which constrains individual particles. The implication here is that some particles join together in a more or less permanent collection, otherwise the 'collection' would only be transient and would depend crucially on the initial conditions. It was one of the serious difficulties of classical physics that there was no inherent dynamical reason why collections should ever form permanently. In quantum mechanics, however, the concept of particle is changed, and the fundamental idea of a continuous wave description of motion produces the 'stationary state' or a local time-independent 'collection' of atoms and

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molecules. Since these local collections are constantly being perturbed, they are not really permanent, but have lifetimes which increase with the energy of the interactions which hold them together, and decrease with the thermal energy which knocks them apart. Although there are several types of bonds between atoms and molecules we will need to distinguish only two – the strong and the weak bonds. The structures held together by the strong chemical bonds will have lifetimes much longer than structures held by weak bonds.

So far our simple physical description is useful up to the level of polymers and crystals, but now we need to see how such collections can 'constrain' *individual* monomers or atoms which make up these collections. Up to this point, our description of matter is 'normal physics' at the level of atoms and molecules, but the concept of 'constraint' begins to sound as if we are introducing new rules. What is the physical meaning of a constraint? The concept of 'equation of constraint' was in fact first necessary in classical physics because of the lack of any dynamical process to explain the permanent loss of degrees of freedom of collections of matter in solid bodies. Another type of constraint is the boundary condition which limits the values of certain degrees of freedom independently of the equations of motion – for example, when a particle is confined by a box. Both solid bodies as well as walls of boxes could be considered as collections of particles which influence the motion of individual particles, and so they fulfil the second condition of our definition of hierarchy. But while we know that solids can form spontaneously from individual particles, constraints such as boxes are usually designed by experimenters with some 'higher' purpose in mind, and in this case our first condition of autonomy would not be satisfied. However, it is primarily the stationary-state solutions of the quantum mechanical equations of motion which account for permanent constraints.

From such apparently simple beginnings we can see the origin of what are often called *structural* hierarchies. The richness as well as the orderliness in all the natural patterns of collections of molecules and crystals could be described as a selective and more or less permanent loss of degrees of freedom among many elements. Many scientists and philosophers will assert on principle that such hierarchical structure is entirely reducible to quantum mechanics. As is often the case, those experts who actually study the details are seldom so easily convinced. For example, Cyril Smith [9] has pointed out that new levels of structural hierarchies usually depend on the appearance of an imperfection in the old level. But what do we mean by an 'imperfection'? Which imperfections lead to new levels of organization, and which lead to greater disorder?

► *Functional hierarchies*. In spite of the enormous complexity which we can find in structural hierarchies, there is still something missing. There is seldom any doubt that such structures are lifeless. What is missing is some recognizable 'function'. No matter how intricate a structure may be, permanence is not compatible with the concept of function. Function is a process in time, and for living systems the appearance of time-dependent function is the essential characteristic of hierarchical organization. To achieve function by permanently removing degrees of freedom in a collection of elements would be impossible. Instead the collection must impose *variable* constraints on the motion of individual elements. In physical language these amount to *time-dependent boundary conditions* on selected degrees of freedom. Furthermore, the time dependence is not imposed by an outside agent, but is inseparable from the dynamics of the system. Such constraints are generally called non-holonomic (non-integrable), and have an effect which is like modifying the laws of motion themselves. For example, the enzyme is not just a permanent linear string of amino acid residues, nor a permanently folded three-dimensional molecule. An enzyme is a time-dependent boundary condition for the substrate, which through the collective interaction of many degrees of freedom controls a few degrees of freedom so as to speed up the formation of a strong bond. Nor is it the essential peculiarity of the enzyme that it is a very *complicated* dynamical system. Any system with as many degrees of freedom as that is complicated dynamically. What is exceptional about the enzyme, and what creates its hierarchical significance, is the *simplicity of its collective function* which results from this detailed complexity.

To put the problem of dynamical hierarchical control in a more general way, it is easy to understand how a simple change in a single variable can result in very complicated changes in a large system of particles. This is the normal physical situation. It is not easy to explain how complicated changes in a large system of particles can repeatedly result in a simple change in a single variable. It is this latter result which we interpret as the 'integrated behavior' or the 'function' of a hierarchical organization. Thus, we find *structural* hierarchies in all nature, both living and lifeless, but *functional* hierarchies we see as the essential characteristic of life, from the enzyme molecule to the brain and its creations.

However our recognition of *function* as having to do with a simple result produced by a complicated dynamical process is not useful unless we can give some physical meaning to the idea of simplicity. The problem is that the concept of simplification is not usually associated with the physical world, but rather with the observer's symbolic representations of this world. The world is the way it is.

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Only an observer can simplify it. In fact it is the assumption that the elementary motions are complete and deterministic that make the generation of hierarchical rules appear so difficult. The hierarchical rule is superimposed upon a lawful system which is already completely deterministic. How can this be done without contradiction?

As far as I can see, this has never been done in physics without introducing what amounts to a measuring device or an observer. Unfortunately, since measuring devices and observers are usually associated with the brain, this does not resolve the contradiction, but only substitutes a human language hierarchy, which is a harder problem than the one we are asking. I want to think of the most elementary configurations of molecules in which we recognize some simple objective function. So again the question arises: How can a lawful system of atoms which is maximally deterministic superimpose an additional functional rule or constraint upon its detailed motions?

And again, the only answer must be that *the concept of functional constraint implies an alternative way of representing the detailed motions*. But in a closed physical system there is no observer to represent the system in a different way. Therefore we are left with the idea that if we can recognize a simple hierarchical function in an isolated dynamical system, then we should also be able to recognize an internal *representation* or *record* of the system's own dynamics. Autonomous hierarchical function implies some form of self-representation. In other words, we may partially resolve the appearance of hierarchical order on an already completely ordered set of elements by saying that hierarchical rules do not apply to the elementary motions themselves but to a record of these motions. Before we look at some examples of simple molecular collections which may exhibit internal records, let us see under what conditions our own hierarchic representations of physical systems arise.

► *Descriptive hierarchies*. The hierarchical levels of our languages contain some of the deepest mysteries of logic as well as epistemology, but I believe they also contain a clue to the physical problem of the hierarchical interface. We have already mentioned the crucial interface between the strictly causal language of dynamics and the probabilistic language of statistical mechanics which has produced much distinguished controversy. I shall try to avoid the intricacies of the general arguments by using a simple example as an illustration.

When we speak of the elementary laws of mechanics we mean the laws that describe as precisely as possible how each degree of freedom changes in time, given the initial conditions and boundary conditions. These equations of motion

are universal and apply to all detailed motions which take place in the system. In one sense, therefore, all additional information about the system is either redundant or contradictory. But if we are trying to describe, say, 10^{23} molecules in a box, it is obvious that measuring or following each degree of freedom is impossible. However, as *outside observers* we have learned to recognize and define collective properties of molecules, such as temperature and pressure, which allow simple and useful measurements on the gas in the box. It is significant that these properties were measured long before their 'molecular basis' was known, just as many hierarchical biological functions were accurately described before a 'molecular basis' was discovered. In physics it was the later discovery of the molecular dynamics which began the controversial attempts to reduce thermodynamical description to mechanical description by rigorous mathematical arguments. Perhaps these attempts can be characterized as very nearly successful – but not quite. This result is not trivial, since 'not quite proved' in mathematics is like 'not quite pregnant' in biology.

We may look at the problem as arising from the inability of the formal mathematics to predict what collective properties of complicated systems will produce simple, significant effects in the physical world of the observer. In other words, while there is no question that the detailed equations of dynamics can be used to calculate previously well-defined averages or collective properties, there is no way to predict from only the dynamical laws of the system which definitions of collective properties are significant in terms of what we actually can measure. Thus in one sense we can derive the pressure in terms of a suitable average of dynamical variables, if we are given a precise definition of pressure; but this definition of pressure is not determined by the equations of dynamics. The concept of pressure appears useful only when the dynamical system is embedded in a particular type of observational environment.

More generally we may say that a physical system which appears complete and deterministic with the most detailed symbolic representation can appear incomplete and probabilistic only with a new representation which relinquishes some of the detail. The new representation must therefore come about through the *combination* or *classification* of the degrees of freedom at the most detailed level so as to result in fewer variables at the new level. Formal reductionism fails simply because the number of possible combinations or classifications is generally immensely larger than the number of degrees of freedom. What must always be added to define a new representation is the rule of combination or classification which tells us how to simplify the details. In statistical mechanics this rule is

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usually a hypothesis of randomness or ergodicity, but the ultimate justification for any such rule is that it results in a more useful description of the system in the observational environment in which the system is embedded.

What can it mean, then, for a collection of particles to form an *internal* simplification or *self*-representation? What is the meaning of an 'observational environment' for a system which is closed? Clearly in an autonomous hierarchy there must be an internal separation of some degrees of freedom from other degrees of freedom which become constrained to impose collective and time-dependent boundary conditions on individual degrees of freedom. While we know such integrated systems exist in cells, and can design machines which operate in this way, we are still baffled by the spontaneous origin of this type of constraint.

It is, in fact, a characteristic difficulty of hierarchical interfaces in biological organizations that their actual operation may appear quite clear while their origin is totally mysterious. The genetic code is a good example of a crucial hierarchical interface that is clear in its operation, but mysterious in its origin. One might wonder, in fact, if there is some inherent reason why a hierarchical organization obscures its own origins. Since it is one general function of hierarchies to simplify a complex situation, Simon [10] has suggested that if there are '... important systems in the world that are complex without being hierarchic, they may to a considerable extent escape our observation and understanding'. Putting it the other way around, I would also suggest that 'being hierarchic' requires that the system control its dynamics through an internal record, which has some aspects of 'self-observation'.

► *The lowest hierarchy.* But this is only evading the question. Let us see if we can clarify the problem of hierarchical origins by looking at collections of molecules of gradually increasing complexity, watching closely for any signs of internal *classification* or *recording* processes which are the essential conditions for a simplification of the detailed dynamics. If we can imagine such collections, then we may go on to ask if this internal simplification is inherently self-perpetuating, or if there appear to be additional conditions which must be satisfied to establish a persistent hierarchical organization of molecules.

Perhaps the simplest interesting level of complexity is crystal growth. First, consider an ideal, ionic crystal growing in solution. One might try to apply our hierarchical conditions by saying that the crystal surface, with its alternating positive and negative sites, 'classifies' the incoming ions, and by permanently binding each ion to a site with the opposite charge forms a 'record' of the classi-

fication interaction. Now while this may be grammatically correct, it is really only a redundant statement. There is no real distinction here between the physical interaction of the ion and the binding site and what we have called the 'classification' and 'record' of this interaction. They are all the same thing. Furthermore, each ion's interaction is local and direct and does not involve the dynamics of any large collection of ions or any delay. Therefore, although we may call this ideal crystal an example of hierarchical structure, I would not say that it exhibits hierarchical control over its dynamics.

Let us go on, then, to a more realistic level. Consider crystal growth which is produced by an imperfection, such as a screw dislocation. This is a *statistical* process which requires more than one atom or molecule to be in metastable positions. In time these atoms would shift to stable positions if there were no further growth. But this screw-dislocation structure increases the rate of growth by many orders of magnitude, all the time maintaining its special structure even though the original collection which first introduced the dislocation has been buried deep within the crystal. In this example, I believe a much stronger case can be made in favor of calling this a kind of hierarchical control. First, the constraint which controls the growth dynamics is not simply the direct interaction between local atoms, but involves the *collection* of atoms which makes up the dislocation. Second, this collection is not the original dislocation, but a *record* of a dislocation which is propagated over time intervals which are very long compared to the rate of addition of the individual atoms. However it is difficult to distinguish a classification process in this example since all the atoms are identical.

As a third, more complicated example, then, imagine a protoenzyme made up of only two types of monomers in a linear chain. Suppose this particular sequence of monomers folds up into a catalyst which speeds up the polymerization of only one type of monomer. For this specific catalytic reaction to occur we must express the fact that the folded polymer can distinguish one type of monomer from the other, and on the basis of this distinction alter the dynamics of each correct type of monomer so that it reacts much faster. Or in other words, we may say that this sequence of monomers *classifies* its elements and *records* this classification by forming a single, permanent bond between monomers. Now is there anything wrong with calling this process a form of hierarchical control?

In so far as the polymer sequences are no longer determined directly by the dynamical laws of the individual monomers (including their inherent reactivities), but by the constraints of a special polymer which speeds up the formation of a

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particular sequence, this might be called hierarchical dynamics. But now I think we have some problems of autonomy. First, this specific catalyst was invented by me, and although we know such specific catalysts do exist as enzymes, my invention simply evades the origin problem, as well as the physical problem of how such specific catalysts work. However, I have in mind a problem which is much more important. I think this example misses the essence of hierarchical *control*. We may indeed have in the catalyzed homopolymer a kind of simple record of a rather complex dynamical interaction, but the record has no further effect.

The trouble is that in the context of autonomous hierarchies, what constitutes a 'record' must be indicated within the closed system itself and not by what I, as an outside observer, recognize as a 'record'. Obviously to generate autonomous hierarchical control the record must be *read out* inside the system. The time-independent constraints formed by the permanent strong bonds must in turn constrain the remaining degrees of freedom in some significant way. This was the case in the previous example of screw-dislocation crystal growth, where the dislocation structure was both a record of a past collective imperfection and a catalyst for the future binding of individual atoms. Cyril Smith sees this process as requiring a new description somewhere in between the detailed dynamics of atoms and the simple, stationary averages of thermodynamics. He sees all complex structure as both a record and a framework: '. . . the advancing interface leaves behind a pattern of structural perfection or imperfection which is both a record of historical events and a framework within which future ones must occur'.

Returning to the copolymer system, we see that it may indeed fulfil the function of a record of past events, but the homopolymer record which was catalyzed does not act as a framework for future events. To provide autonomous hierarchical control, the catalyzed product of one copolymer must lead to the catalysis of other specific reactions. Furthermore, if the record is not to be lost, each catalyzed sequence must in turn catalyze another, and so on indefinitely. Now clearly such a sequential process can be divergent or convergent depending on the rules of specificity for the catalyses. Even if we assume that there is no error in these rules, a divergent record would never be recognized. One might say, in this case, that the system's self-representation is as complex as the system itself. But I think no *underconstrained* system would produce such a chain of catalyses. The starting record would simply disintegrate.

Going back now to the hierarchical control in the screw-dislocation crystal

growth, we may look at this example as the other extreme. Here the classification and record possibilities are trivially *overconstrained*. Since there is only one distinguishable type of monomer, there can be no classification and hence no linear record. The 'record' is not distinguishable from the three-dimensional structure which is also the functional catalytic site. The same problem of *overconstraint* could, of course, occur in a copolymer system where, say, an alternating-sequence polymer acts as a tactic catalyst for the same alternating sequence. But this is the point of these examples. I want to show that even the simplest hierarchical organization requires a balance between the numbers of degrees of freedom of its elements, the number of fixed constraints, which function as a record, and the number of flexible constraints which encode or transcribe the record.

Of course from this simplest conceivable level of molecular assembly which exhibits a potential *classification-record-control* process, we should not expect to find the nature of hierarchical interfaces at *all* levels. Even these simple examples present unanswered questions. But in following the necessary physical steps leading from the dynamics of individual units to the collective control of individual units, I believe we can gain some insight into the spontaneous generation of hierarchical organization.

First, we see that the individual particles or units follow more or less deterministic laws of motion. These units were atoms or molecules in my examples, but we may also think of the units as cells, multicellular individuals, or population units. The 'motions' of these larger units are not as deterministic as the motion of atoms, but they have definite patterns of unit behavior. Second, there are forces between units which produce constraints on the individuals. These forces cause permanent aggregations of units which act as relatively fixed boundary conditions on the remaining individuals. By 'relatively fixed' I mean that the rate of growth or change of these aggregations is slow compared to the detailed motions of individual units. These strong forces form what we called structural hierarchies, but they are essentially passive constraints.

The third stage is crucial and, as we might expect, the most mysterious. If the fixed constraints are not too numerous, that is, if the aggregations are not too rigid, then *weak forces* become important in the internal dynamics of the aggregations and through this *collective* dynamics the aggregations can form *time-dependent boundary conditions* for the other individual units. This type of flexible or non-holonomic constraint reduces the number of possible trajectories of individual units without reducing the number of degrees of freedom. This amounts

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to a *classification of alternatives* which leads us now to use the higher language of information or control. The specific catalyst or enzyme is the simplest example of such a dynamical constraint; but at any level of hierarchical control where there are ordinary molecules which also act as messages, or where simple physical objects are said to convey information, there must be the equivalent of such dynamical constraints which classify alternative motions by leaving a record of their collective dynamical interactions.

. As we said earlier, it is in the simplicity or relevance of these records or messages that we recognize hierarchical control; but how this simplicity originates remains a mystery. In practice, when a dynamically complex system exhibits simple outputs or records of its internal motions we switch languages from the detailed dynamical description to a higher language, which relinquishes details and speaks only of the records themselves. We might think of our simplified language as an *effect* necessitated by a system that is too complicated to follow in detail, as in the case of our thermodynamic description of a gas. On the other hand, in systems which exhibit autonomous hierarchical organization, it is the internal collective simplifications which are the *cause* of the organization itself. In this sense, then, a new hierarchical level is created by a new hierarchical language. Simon [10] has come to a similar conclusion from observing a broad class of hierarchical organizations. He calls the lower level language a detailed 'state description' and the upper level language a simple 'process description'. But the fact remains that whether it is the system-observer interface in physics, the structure-function interfaces in biology, or the matter-record interface in the most primitive molecular hierarchies, these levels are presently established only at the cost of creating separate languages for each level.

► *Conclusion.* I have described the simplest examples I can imagine of what might be called incipient molecular hierarchies. I have used only a rough, semi-classical language, and have not even touched on the crucial question of how specific catalysis or classification processes could be described in the deeper quantum mechanical language. Nevertheless, I find the physical concreteness of these simple examples very helpful in sorting out which conditions are most essential for establishing a hierarchical interface.

What we find is that even the lowest interesting example of a hierarchical interface is beset with precisely those difficulties that we find in all hierarchical structures, namely, that each side of the interface requires a special language. The lower level language is necessary to give what we might call the legal details, but the upper level language is needed to classify what is significant. As

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Polanyi [8] has so clearly pointed out, living organizations are not distinguished from inanimate matter because they follow laws of physics and chemistry, but because they follow the constraints of these internal, hierarchical languages.

It is therefore difficult for me to escape the conclusion that to understand even the simplest biological hierarchies, we will have to understand what we mean by a record or a language in terms of a lower level language, or ultimately in terms of elementary physical concepts. Physicists have worried about the inverse problem for many years. In fact a large part of what is called theoretical physics is a study of formal languages, searching for clear and consistent interpretations of experimental observations. Biologists have never paid this much attention to language, and even today most molecular biologists believe that the 'facts speak for themselves'. Hopefully, as these facts collect, biologists, too, will seek some general interpretations. All these facts tell us at present is that life is distinguished from inanimate matter by exceptional dynamical constraints or controls which have no clear physical explanation. We will not find such an explanation by inventing new words for *our* description of each level of hierarchical control. Instead, we will have to learn how collections of matter produce *their* own internal descriptions.

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Notes and References

1. All the authors on molecular biology I have read tacitly assume that the classical idea of a deterministic machine is a good physical analogy to living matter, even though living parts are more flexible than most machine parts, e.g., D. E. Wooldridge, *The Machinery of Life* (McGraw-Hill: New York 1966). No one, except Polanyi [8], points out that machines are only designed and built by man, and are therefore a biological rather than a physical analogy.
2. H. H. Pattee, The physical basis of coding and reliability in biological evolution, in (C. H. Waddington, ed.) *Towards a Theoretical Biology 1: Prolegomena* p. 67 (Edinburgh University Press 1968).
3. This idea was popularized largely by E. Schrödinger's book *What is Life?* (Cambridge University Press 1945). Also see N. Bohr, *Atomic Physics and Human*

- Knowledge* pp. 21 and 101 (John Wiley and Sons: New York 1958); F. London, *Superfluids* (2nd ed.) vol. 1 p. 8 (Dover Publ.: New York 1961); and E. P. Wigner in *The Logic of Personal Knowledge* p. 231. (Routledge and Kegan Paul: London 1961).
4. There are so many papers on the measurement process, I shall give only two older references, N. Bohr, *Phys. Rev.* 48 (1935) 696; and J. von Neumann, *Mathematical Foundations of Quantum Mechanics* Chap. V (Princeton University Press 1949); and one more recent paper, E. Wigner, *Am. J. Phys.* 31 (1963) 6.
5. H. H. Pattee, Physical problems of heredity and evolution, in (C. H. Waddington, ed.) *Towards a Theoretical Biology 2: Sketches* p. 268 (Edinburgh University Press 1969).
6. This point of view, well known to classical

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biologists, is brought out sharply by Paul Weiss, From cell to molecule, in (J. M. Allen, ed.) *The Molecular Control of Cellular Activity* p. 1 (McGraw-Hill: New York 1962). Epitomizing the nature of hierarchical organization, Weiss says, 'In short, the story of "molecular control of cellular activities" is bound to remain fragmentary and incomplete unless it is matched by knowledge of what makes a cell the unit that it is, namely, the "cellular control of molecular activities" '.

7. F. Crick, *Of Molecules and Men* (University of Washington Press: Seattle 1966).

8. M. Polanyi, Life's Irreducible Structure, *Science* 160 (1968) 1308.

9. C. S. Smith, Matter Versus Materials: A Historical View, *Science* 162 (1968) 637.

10. H. A. Simon, The Architecture of Complexity, *Proc. Amer. Philos. Soc.* 106 (1962) 467. In addition to emphasizing the essential correlation between state and process languages in any functional hierarchy, Simon characterizes hierarchical organizations as 'nearly decomposable', by which he means that the state space is larger than the trajectory space. This is nearly equivalent to what I call a non-holonomic constraint.

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