THE PHYSICAL BASIS OF CODING AND RELIABILITY IN BIOLOGICAL EVOLUTION

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CONTENTS

I. What is a Theory of Biology?

Within the intellectual discipline of the physicist there has developed a belief in the existence of general and universal theories of nature, and it is the search for such theories which may be said to guide and justify the intellectual efforts of the physicist as well as the design of most physics experiments. What a physicist means by a "good theory" cannot be exhaustively spelled out. Of course it must include "fitting the data" or "predicting observations" in some general sense. However, much deeper and more obscure criteria are also applied, often tacitly or intuitively, to evaluate the quality of a physical theory. For example, general theories can never be "just so" stories which are only built up bit by bit as data accumulate. General physical theories often stem from relatively simple hypotheses which can be checked by experiment, such as the constancy of the speed of light and the discrete energies of photons from atoms, but they must also be founded upon broad principles which express concepts of conservation, invariance, or symmetry. These abstract principles come to be accepted because from our experience we find that in some sense they appear unavoidable. In other words, without such principles it is difficult even to imagine what we mean by a general physical theory of the universe (1).

Traditionally, in biology, the relation of theory to experiment has been more remote. Much of what is sometimes called biological theory appears to the physicist as a "just so" story since it is often only a mathematical formalism designed for the practical solution of a specific type of problem and has no direct relation to general physical laws. This situation is often ascribed to basic differences in the subject matter of the physical and life sciences. Perhaps this lack of a basic biological theory is at the root of unresolved historical vitalist-mechanist arguments, since much biological terminology never even makes contact with the language of physics.

But recently, following the so-called molecular biological revolution, there have been many statements that now, at last, the mystery of life has

indeed been reduced to physical language and laws. In particular we find biochemists and molecular geneticists claiming that they have shown that normal physical and chemical laws provide a relatively clear and simple basis for understanding heredity and most aspects of metabolism. The Watson-Crick template DNA model is commonly accepted as the central concept which is said to reveal the mystery of heredity (2), and similarly, the detailed structure of proteins has been said to provide a basic understanding of enzyme mechanisms (3). A common working assumption of molecular biologists is that the remaining problems will be solved by additional experiments. In any case, they do not see any obstacles or essential mysteries on the horizon (4). This leads to the attitude that biology is explained in terms of ordinary existing physical laws and that therefore no great effort is necessary to apply physical theory to living matter.

On the other hand, in spite of these detailed factual descriptions of polynucleotide and polypeptide interactions in the cell, many physicists as well as biologists remain uneasy. Is this vast amount of phenomenological description really sufficient to support the claim, which is now made even in elementary biology textbooks, that we have a fundamental understanding of living matter in terms of physical laws -- that heredity has proven, after all, to be extraordinarily simple, and that the remaining unknowns about living matter are only details to be filled in by more experiment? Can we say with justification that we understand how the laws of physics explain the essential nature of life?

In the remainder of this paper I shall attempt to express why this claim that biology has now been understood in terms of physical laws is not yet convincing. I shall also give some reasons for concluding that the central mysteries of living matter are not to be solved only by collecting more data. Furthermore, I shall propose that even to make a basic distinction between living and nonliving matter, some fundamental logical and physical problems remain to be solved at the quantum mechanical level. In particular, I shall argue that any fundamental theory of biology must describe the physical basis of enzymatically-controlled hereditary processes which possess the reliability necessary for evolution, and that this will require what amounts to a deeper

understanding of the quantum theory of a molecular measurement process.

II. Current Molecular Biological Descriptions

There is no need here to repeat in any detail the descriptions used in modern molecular biology since so many reviews are now available. By molecular biological description we shall mean the use of such concepts as the template replication of DNA, the transcription of the genetic message from DNA to messenger RNA, the translation of this coded message to amino acids and the synthesis of proteins (5). An enormous amount of detail is now known about these processes and much more will undoubtedly be discovered in the near future. The principle question, however, does not have to do with the quantity or quality of these data, but rather with their physical interpretation. In particular we want to discuss whether or not these molecular biological descriptions allow us to conclude that the nature of living matter can now be understood in terms of the general laws of physics.

Normally when the physicist says he understands, say, the chemical bond in terms of general physical laws, he does not mean simply that he is optimistic that chemical bonds are consistent with quantum mechanics or that if he cared to go into the matter he would find no serious problem in describing the chemical bond by the rules of quantum mechanics. On the contrary, although the chemical bond was first recognized and discussed at great length in classical terms, most physicists regarded the nature of the chemical bond as a profound mystery until Heitler and London quantitatively derived the exchange interaction and showed that this quantum mechanical behavior accounted for the observed properties of valency and stability. On the other hand it is not uncommon to find molecular biologists using a classical description of DNA replication and coding to justify the statement that living cells obey the laws of physics without ever once putting down a law of physics or showing quantitatively how these laws are obeyed by these processes. Of course, as a speculative prediction such statements are acceptable But certainly nothing could be less fruitful than allowing this most fundamental and

challenging question of whether living matter can be reduced to the basic laws of physics to be obscured by such pronouncements from molecular biologists, without some regard for the established language and laws of physics.

III. What is the Question?

Let us for the moment, however, assume that the experiments of molecular biology and genetics have indeed shown that no detailed process in living matter evades or violates normal laws of physics. If this were the case, does the question of the nature of life appear answered? In other words, even if it were the case that living matter was exactly the same as nonliving matter with respect to description by physical laws, would we then say that we fully understand life in terms of physical laws? No, I think not, because this does not answer the obvious question of why living matter is so conspicuously <u>different</u> from nonliving matter. In other words, we do not find the physical similarity of living and nonliving matter so puzzling as the observable differences. Before we can attempt to explain these differences in terms of physical laws we must state clearly what these differences are. Older biology texts usually begin by listing the "characteristics of life" which may include growth, reproduction, irritability, metabolism, etc., but these are not general enough concepts. What is the most general property of life which distinguishes it from nonliving matter? Certainly the most <u>general</u> property is the potential to evolve. Therefore, the fundamental question can be restated: Is the process of biological evolution understandable in terms of basic laws of physics?

IV. Two Basic Assumptions

In order to show the difficulties in answering this question let us restate the situation in the form of assumptions:

Assumption A. Living states and nonliving states of matter are in no way distinguishable by their detailed description in terms of initial conditions or elementary laws of motion, i.e., both living and nonliving forms of matter obey precisely the same physical laws.

Assumption B. Living states of matter are distinguishable from nonliving states of matter only by the potential for evolution, i.e., the hereditary transmission of naturally-selected traits.

To make these assumptions more plausible let us consider for a moment the antithetical assumptions. Suppose, for example, that the difference between living and nonliving matter depended upon different initial conditions. From the point of view of the physicist we would have to call this a "special creation" which may be allowable as a highly unlikely event or a miracle; but this would nevertheless be scientifically barren since it can neither be derived from any physical theory nor tested by any real experiment (6). Furthermore, if we assumed that living and nonliving matter obey different elementary laws of motion, then by the physicist's meaning of a law there must be observable or derivable regularities or correlations between detailed measurements involving one type of matter but not the other. Since an enormous number of observations have been made and no such regularities have been found, this antithetical assumption seems unjustified. Notice that Assumption A does not imply that all aspects of physical theory have been formulated, but only that whatever theories we currently accept must apply equally to living as well as nonliving matter. Finally, if we reject Assumption B and assume antithetically that living and nonliving matter can both evolve in some sense, then we have only succeeded in generating a new question: Why did living matter distinguish itself by evolving so much more variety than nonliving matter? In other words, we must have in addition to Assumption A, which states the similarity of nonliving and living matter, a second assumption which clearly distinguishes living from nonliving matter. To omit the second type of assumption is to miss the whole problem.

Accepting Assumptions A and B for our discussion, what can we conclude from them? Some physicists feel that such assumptions are contradictory. Wigner's (7) argument that self-replication is impossible, assuming only the normal laws of quantum mechanics, would fall into this category. Other physicists propose that autonomous biological laws must exist. Such arguments have been given by Bohr (8), Elsasser (9), and Burgers (10), for example.

My own point of view is that there is no scientific value whatever in attempts to dismiss such arguments because they have their basis more in the language or logic of physics rather than in the details of molecular biology. Assumptions A and B are statements of a crucial paradox which must be zealously and carefully pursued if we are to have a physical theory of general biology. Furthermore, I believe there is reason to expect that these assumptions are closely related to the central epistomological paradox of the mind-body problem itself. However, in this paper I shall emphasize this paradox only in the context of the origin of life problem. First, I shall try to clarify these assumptions so as to sharpen the paradox. Otherwise the central problem can too easily become obscured by the many details of new experimental discoveries.

V. What are the Physical Laws?

The Assumption A is relatively easy to amplify because the meaning of initial conditions and laws of physics have already been deeply analyzed (11). What we wish to emphasize, however, is that the physicists's meaning of "obeying the laws of motion" is a rigorous statement which can be quantitatively verified by measurement and calculation. An elementary law of motion is a prescription for correlating the values of certain variables which give the state of a system at any one time to the values of these variables for any other time. In this language, once the complete state of a given system has been chosen by assigning initial conditions for one time, any additional information about an earlier or later state of the system is redundant. That is, no better prediction about the future or past of the system can be made, in principle, by

supplying more information. The rules for applying this descriptive language are precisely formulated and one cannot, for example, say that a molecule obeys these elementary dynamical laws of physics simply by looking at numbers representing the <u>average</u> structure of a large collection of these molecules or by moving around a desk-top classical model of one of these molecules. In other words, to say that an enzyme or nucleic acid molecule obeys the dynamical equation of motion of quantum mechanics cannot be regarded by the physicist as a justifiable conclusion without some evidence to actually support such statements.

We have therefore labeled our statement A as an Assumption, because although it might be argued that quantum mechanics has in the past described correctly many diverse molecular effects, we must also consider the arguments that have been presented showing that quantum mechanics is not consistent with the basic property of self-replication.

In the clarification of Assumption B we encounter another type of difficulty. Few biologists would dispute that the living states of matter evolve by a different process than the nonliving states. In fact, the potential for hereditary evolution may be used as a definition of present life. But it might be argued that hereditary evolution is not the most elementary or fundamental condition for the origin of life. For example, simple autocatalysis, metabolism, or replicating processes may also be called primeval features of the living state. However, to be brief, I shall simply define as a necessary condition for the origin and persistence of life the property of reliable hereditary transmission of naturally-selected traits. Unfortunately this phrase is not yet in the language of physics, and its meaning is often imprecise even in biology. Therefore, let us try to define what hereditary transmission and natural selection can mean in the language of physics.

VI. What is Heredity?

The traditional idea of a hereditary process involves the transmission from parent to offspring of particular traits. By a trait the biologist does not mean an invariant of the equations of motion, but

one property chosen from a set of possible alternatives. The trait which is actually transmitted depends upon a description of the trait recorded or remembered from some earlier time. Thus, the central biological aspect of hereditary evolution is that the process of natural selection operates on the actual traits or phenotypes and not on the particular description of this phenotype in the memory storage which is usually called the gene. This is essential biologically because it allows the internal description or memory to exist as a kind of virtual state which is isolated for a finite lifetime, usually at least the generation time, from the direct interaction which the phenotype must continuously face.

The crucial logical point of hereditary propagation which corresponds to the biological distinction between genotype and phenotype, is that hereditary propagation involves a description or code and therefore must require a classification of alternatives and not simply the operation of the inexorable physical laws of motion on a set of initial conditions. As we stated in the last section, these laws of motion tell us how to transform the state of a system at a given time into the state at any other time in a unique and definite way. The equations of motion are therefore said to perform a one-to-one mapping, or more specifically, a group transformation of the states of a system. On the other hand, the hereditary process which must transmit a particular trait from a larger set of alternatives must perform a classification process, and this involves a many-to-one mapping. It is for this reason that concepts such as memory, description, and code which are fundamental in hereditary language are not directly expressible in terms of elementary physical laws. Direct copying processes, such as crystal growth or complementary base pairing in DNA, do not involve a code or classification of alternatives; and therefore, even in classical language, simple template copying processes are not a sufficient condition for evolution by natural selection. When there is no distinction between genotype and phenotype or between the description of a trait and the trait itself or, in other words, when there is no coding process which connects the description by a many-one mapping with what is described, then there can be no process of hereditary evolution by natural selection.

The logical aspects of this fundamental evolutionary principle were understood by von Neumann (12) in his design of a self-replicating automaton based on the Turing machine. It is significant that von Neumann's self-replicating automaton has the same basic logic that is now known to exist in cells, even though his replicating automaton was designed without any knowledge of the details of the cellular translation code and the roles of nucleic acids and enzymes. Nevertheless it was clear to von Neumann that simple template replication or copying in itself was of no interest in either the logical or the evolutionary sense, and that only a concept of heredity which includes a code could provide growth of complexity that had any real significance for learning and evolution. Thus it may be said that a threshold of logical complexity exists for the origin of evolving hereditary structures. Following von Neumann's work many papers have pursued the interesting and essential logic of this problem (13). It is remarkable how few biologists are aware of this work and of the logical basis for a coding process in hereditary transmission, as well as the broader significance of a genotype and phenotype in biological evolution.

VII. The Central Problem

We have now given some idea why the elementary laws of physics do not seem directly suitable for describing hereditary behavior. At the logical level we may say that the laws of physics describe a one-to-one mapping process, whereas hereditary propagation requires a many-to-one mapping process. Or in more physical terms we may say that the elementary physical laws are symmetric with respect to time, whereas hereditary propagation requires a direction to time. Or in other words, the temporal relation between the memory of a trait and a trait itself is not symmetric.

There is of course a broad general theory of physics called thermodynamics which is capable of treating irreversible phenomena. We may therefore ask if thermodynamic or statistical mechanical theories cannot be applied to hereditary phenomena. The answer is that of course

they can be applied, but they do not lead us to expect biological evolution. In fact, it is the second law of thermodynamics which at first sight appears to be the antithesis of biological evolution leading as it does to complete disorder as opposed to the increasing complexity of biological organisms. We may therefore say that the problem of describing hereditary processes in terms of the laws of physics must not only overcome the difficulty in deriving irreversible phenomena from reversible laws, but in addition it must also show how the consequences of hereditary irreversibility lead to the phenomenon of evolution in living matter rather than the complete thermodynamic equilibrium of nonliving matter.

VIII. The Classical Evasion of the Central Problem

One popular concept of living matter which seems to evade this paradox is the co-called automata description of molecular biology. This description treats the cell as a classical machine which behaves very much like a modern large-scale computer (14). Such classical machines clearly exhibit the property of memory storage and hereditary transmission as well as coding and classification processes. How are such classical machines described in terms of the laws of physics?

This can be done only by the introduction of a certain type of structure which controls to some extent the dynamic motion of the system, but which is not derivable directly from the basic equations of motion. In order to exhibit the fundamental hereditary property of classification, or the selection of a trait from a larger set of alternative traits, there must be available more degrees of freedom in the static description of the machine than are available for the dynamic motion of the machine. In other words, the very concept of a memory in a hereditary system implies the existence of more freedom in the static state description than in the motion of the system, since it must be dynamically constrained so as to propagate only that particular trait which is recorded in the memory storage. Such a structure which has more degrees of freedom in its state description than in its dynamic motion is called in classical physics a <u>non-holonomic</u> constraint (15). If one accepts the classical

description of non-holonomic constraints, it is possible to tailor a machine to represent almost any code or logical function which one can imagine, and this is the basis of all computer design. In fact, it is possible to program large-scale digital computers to imitate macromolecular processes in living cells, including DNA replication, transcription, and coding into protein enzymes (16). We therefore must raise the question: Are classical descriptions or models of living cells an adequate basis for understanding the fundamental nature of living matter and its evolution?

A part of the answer to this question was already suggested by the physicist, Schrödinger (17), in his book, "What is Life?" which appeared in 1944. Schrödinger pointed out that the order which we associate with classical mechanisms is based on the averages of large numbers of molecules, whereas the order in the cell is based on single molecules. Schrödinger suggested that the relative stability of individual molecules can be understood in terms of the stationary states of quantum mechanical systems, but he did not discuss the transmission of this order into macroscopic systems, that is, the expression of this order as a hereditary trait. This is another statement of the central problem which still must be solved.

In order to present the problem in more detail, let us return to the classical concept of a hereditary system which must involve a non-holonomic constraint. What are some of the basic properties of non-holonomic systems? The idea of a constraint is entirely classical, arising from the treatment of some degrees of freedom as purely geometrical structures which do not depend on time and the laws of motion. However, when we look at matter in more detail, we realize that all macroscopic structures must ultimately be represented by elementary forces which hold them together. We may then distinguish permanent structures as only metastable configurations with relatively long relaxation times compared to our time of observation. For example, an ordinary clock which may, during short intervals, appear to be telling very accurate time will, over longer intervals, slowly lose this accuracy and gradually approach irreversibly the equilibrium to which all classical machines must tend. A good clock is simply a mechanical device which

manages to measure the same time interval a large number of times before it reaches equilibrium. Thus at least two widely differing relaxation time scales are necessary for the description of hereditary behavior in statistical systems, and at least one of these time scales must describe an irreversible process. Usually one of these time scales is so long that it is neglected in the treatment of the dynamical problem, and it is replaced only by geometric constraints. The more complete mathematical description of this classical hereditary behavior in nonequilibrium, nonlinear statistical mechanical systems can become very elaborate (18). But, as Schrödinger pointed out in the case of hereditary storage, the peculiarity of biological chemistry is that all its hereditary processes are based on the dynamics of individual molecules and not on statistical averages of vast numbers of molecules. Therefore we must try to extend these classical and statistical mechanical ideas of a hereditary process to individual reactions at the quantum mechanical level.

But in view of the obvious difficulty of such a microscopic description we may again raise the question: Why is it necessary to use quantum mechanical description when it is known that in many cases, even in chemistry, a classical description is adequate for a good understanding of the processes involved? In other words, why is it not possible to admit that a quantum mechanical description would indeed be more accurate, but that for all practical purposes a classical description is close enough?

IX. The Reliability Condition for Evolution

Now we have asked the crucial question: When is a theory or a description "close enough"? We have asked this question about our own attempts at describing living matter in terms of physical laws; but certainly the same question can be applied to the hereditary process itself, and we may ask: When is the description of a hereditary trait "close enough"? This is a very practical type of question, and its answer depends upon what purpose one has in mind for a particular theory or hereditary description. In the context of the origin of life

we may restate this question as follows: When is hereditary storage and transmission reliable enough to achieve the persistent evolution of complexity in the face of thermodynamic errors, that is, in the face of the second law of thermodynamics? Even though we do not understand the mechanism, the only conclusion I have been able to justify is that living matter has distinguished itself from nonliving matter by its ability to achieve greater reliability in its molecular hereditary storage and transmission processes than is obtainable in any thermodynamic or classical system.

Now while it is reasonable to assume that the relatively high reliability of hereditary storage in cells is based upon the quantum mechanical stationary states of single molecules, we must still find an explanation for the relatively high reliability of the expression of these hereditary descriptions as classical traits which interact with the classical environment. In other words we may say that the description of the trait is quantum mechanical, whereas the natural selection takes place on the classical level between the phenotype and the environment. But even though we do not understand the hereditary transmission process, the answer to our question whether classical laws are "close enough" for a theory of life is now obvious; for if the cell itself cannot use a classical description for its hereditary processes, then how could we expect to describe this unique biological reliability only in terms of classical description?

We must next ask what type of physical theory can be used to describe the expression of a quantum mechanical hereditary description as classical interactions between the phenotype and the environment. In particular, by what physical theory do we describe the hereditary transmission process which decodes the quantum mechanical description to produce the classical phenotypic expression?

X. The Quantum Theory of Measurement

There are a few other types of phenomena in physics in which quantum and classical descriptions must be closely related--ferromagnetism,

low temperature phenomena, such as super-conductivity and super-fluidity, and the measurement process in quantum mechanical systems. It is significant that for all these types of phenomena there exists no complete description in terms of elementary quantum mechanical equations of motion. For this reason, while it does not appear likely that an explanation of molecular hereditary transmission will be produced forthwith, at least the problem is not entirely foreign to physics. Therefore while I cannot support the optimistic belief of many molecular biologists that heredity is simple and has now been explained in terms of physics, neither can I be as pessimistic as some physicists in their assertion that living states of matter cannot be derived from physical laws.

The problem of describing a measurement process in terms of the quantum equations of motion has evaded clarification since the formulation of quantum mechanics. Since there are many papers which discuss the problem in detail (19), I shall do no more here than suggest how molecular hereditary processes are related to the quantum theory of measurement. The basic problem may be stated in the following way: The quantum equations of motion operate on unobservable wave functions which may be interpreted as probability amplitudes. Under certain conditions, these unobservable probability amplitudes can be correlated with observable variables in the normal classical world, and when this happens we can say that a quantum mechanical measurement has been executed. However, the quantum equations of motion do not appear to account for this correlation of probability amplitudes with the observable probabilities in the classical world, and a second type of transformation called "the reduction of the wave function" must be used to produce a measurable quantity. The quantum equations of motion are reversible in time and perform a one-to-one transformation of the wave functions, whereas the reduction of the wave function or measurement is an irreversible process and involves a classification of alternatives or a many-to-one transformation. This necessity for two modes of description is at the root of the wave-particle duality, the uncertainty principle, and the idea of the necessity of complementarity in the complete description of quantum events.

However, it is also this duality which leads to the conceptual difficulties of measurement processes, since there is as yet no objective

procedure for specifying where in a chain of events a measurement occurs. In other words, whether or not a measurement is said to occur depends somewhat arbitrarily on where the observer chooses to separate his quantum mechanical and classical descriptions of a given measurement situation. If he chooses to consider the entire system, including what he would normally call the measuring instrument, as only a single quantum mechanical system, then he could recognize no measurement. In the same way, if he chooses to treat a collection of molecules which includes what he normally would call a hereditary memory as only a single quantum mechanical system, then he could recognize no hereditary process (20).

XI. Enzymes as Measuring Molecules

In view of the unsatisfactory state of the theory of measurement in quantum mechanics, it is a remarkable fact that physicists continue to make accurate measurements, just as biologists continue to replicate, without, in a sense, understanding what they are doing. However, in the case of physicists this can be partially explained by the size of measuring devices which are usually large enough to be clearly recognized and treated only as classical systems. In any case, measuring devices are designed by men and are not considered as spontaneous collections of matter. On the other hand, we cannot make this excuse for biological replication. When we speak of individual molecular hereditary transmission as similar to a measurement process, we must ask what corresponds to the measuring instrument at this microscopic level. Or in terms of the origin of life, what is the simplest molecular configuration which could express a hereditary trait and which we could have expected as a reasonable spontaneous molecular organization?

Here we must return to our fundamental definition of heredity as a classification process rather than as simple copying, or the propagation of an invariant of the motion. We have pointed out that a classical physical representation of a classification process must depend on non-holonomic constraints, that is, on structures which allow more degrees of freedom in the state description than is available for the

actual dynamic motion of the system. At the molecular level this would imply that non-holonomic constraints allow a larger number of energetically possible reactions than the number of reactions which are actually available to the dynamics of the system. Now in chemical terms, reactions which are available as distinct from those which are energetically possible, can differ only in the activation energy and entropy, so that we are led to associate the classification process or hereditary propagation with the control of rates of specific types of chemical reactions. Of course in cells the control of rates and specificity is accomplished by the enzyme molecules. Furthermore, it is significant that classical models of enzyme mechanisms depend upon flexible structures or allosteric (21) and induced-fit (22) descriptions which are equivalent to the physicists' non-holonomic constraints. It is of course possible that other molecules such as nucleic acids also exhibit non-holonomic, catalytic properties, but this remains to be demonstrated.

As we have already noted, the physicist may design and perform experiments on quantum mechanical systems without microscopic analysis of the process of measurement, since in most cases a distinction between the quantum system being measured and the classical measuring device can be clearly specified or recognized. In other words, we accept the non-holonomic constraints of a clock, a switch, or gate mechanism because these are large classical devices with many degrees of freedom which we can statistically tailor to approximate our needs with the desired precision or reliability. But at the microscopic level it is by no means obvious that we could design a single molecule which performs with the speed and reliability observed for specific enzyme-controlled reactions. In the first place, the very idea of a non-holonomic constraint in an elementary quantum mechanical system forces on us a profound modification of the language (23). Not only would the idea of measurement have to be extended to include non-observed quantities, but also the equations of motion are effectively modified by non-holonomic conditions, since there is no possibility in deriving such exact constraints by taking into account additional existing degrees of freedom. On the other hand, this requirement of a reliable microscopic non-holonomic constraint is consistent with the early suggestion of London (24), and more recent suggestion of

Little (25), that macromolecules could conceivably possess superfluid or superconductive states which would allow change of shape or transfer of matter with no dissipation. As London pointed out, such a quantum fluid state would combine the characteristic stability of stationary states with the possibility of dynamic motion isolated from thermal agitation. This is precisely what would appear to be essential for specific catalysts which act as precise molecular measuring devices.

A direct experimental test of such a measurement theory of specific catalysis may run into a type of difficulty foreseen by Bohr, namely that external measurements of crucial life processes may be incompatible with the results of the process. If measurements by single enzyme molecules depend upon the internal correlation of their electrons, then any device which can be said to perform an external measurement on these electrons will necessarily destroy some of these correlations with the result that specificity and catalytic power of the enzyme will be correspondingly decreased. However it is not clear that other more indirect evidence may not be obtained to test such a theory (26).

It is to be expected, of course, that classical description will indeed be useful at many points, and that for many practical applications the details of the quantum mechanical description are unnecessary. However, in terms of any general theory of biological systems the reliability of hereditary transmission or the speed and accuracy of measurement is crucial. For example, the difference between a mutation rate of 10^{-4} and 10^{-8} per elementary hereditary transmission may easily be the difference between the immediate extinction or long evolution of a species, and no one could claim that this is a trivial difference (27). It is this quantitative difference in the speed and reliability of hereditary transmission for which quantum mechanics can account and for which classical theory cannot.

In terms of the origin of life problem, this assumption also leads us to believe that life began with a catalytic coding process at the individual molecular level, since no spontaneous thermodynamic system, or classical machine appears to provide the necessary speed and reliability for such a distinctive evolutionary process within the classical environment. Therefore, although with great effort we may design complicated classical hereditary machines which may adapt themselves

to a classical environment for a limited time, we would not expect such complex devices to arise spontaneously on the primitive earth, nor could we expect them to achieve a statistical reliability in their hereditary processes, which would allow them to distinguish themselves so successfully from the environment for five billion years.

XII. Design of Origin of Life Experiments

What type of abiological experiments does this measurement theory of hereditary processes suggest? First of all we are led to believe that specific catalytic molecules are essential for the coding process in hereditary transmission. Contrary to the so-called central dogma which states that nucleic acids transmit all hereditary information and that proteins can only receive it, we would have to conclude that while template molecules or holonomic structures may be said to <u>store</u> hereditary information, it is only the non-holonomic or allosteric catalysts which can <u>transmit</u> hereditary information. Moreover, it is important to realize that <u>a definition of stored information itself cannot usefully be made without a complete specification of the coding mechanism for transmitting it</u>. Without complete specification of the transmission code there is no way to determine what variables of a given physical structure consist of hereditary information which is to be transmitted, and what variables are simply to be treated as initial conditions needed to specify the storage structure at a given time. Failure to recognize that prior specification of the transmission code is necessary in order to define stored information in an objective way has led to much confusion in the use of the information concept, particularly in biological systems.

The experimental approach suggested by this theory contrasts sharply with the strategy of most so-called "chemical evolution" or abiogenic organic synthesis experiments which emphasize the growth of non-hereditary chemical complexity as judged by the similarity of particular spontaneous species of molecule with existing biochemical species in cells (28). While it may be relatively easy to compare the similarity

of these spontaneous molecules with the evolved molecules of cells, the question of the significance of each type of molecule is left open. This has generated much discussion as to which type of synthesis is most closely related to the origin of life on earth and elsewhere. Since widely different sets of initial conditions can produce many of the same organic molecules, there have also arisen controversies over such uncertainties as the equilibrium conditions and free energy sources which actually produced the first prebiological molecules on the earth, and what extraterrestrial conditions might favor the occurence of certain types of prebiological molecules.

I would like to point out that from the hereditary point of view it makes little difference for the general origin of life problem whether a molecule is made by heat, ultraviolet, ionizing particles, or for that matter obtained from a chemical supply house, as long as the molecule has no memory. Furthermore, since we can associate hereditary transmission only with rate control processes, or, in other words, since equilibrium states can have no memory, we should not expect equilibrium conditions to play a primary role in the origin of life. Of course I do not mean that organic syntheses and equilibrium considerations are not important for the origin of life problem. What I wish to emphasize is that the hereditary property itself is the only context from which these other questions can have any objective biological intepretation. Our theory therefore constrains us to look for the simplest possible hereditary chemical reaction processes before we can usefully compare our chemical products with living cells.

XIII. Examples of Hereditary Copolymer Reactions

How shall we experimentally recognize the most primitive hereditary reactions or codes in simple molecules? This is a very difficult question which I cannot fully define, but the general idea can be illustrated by a series of examples of polymer growth. Consider first a simple growing homopolymer in which there is an initial monomer addition rate constant, K_a . After the chain grows long enough, suppose

that it folds into a helical conformation, say, with five monomers per turn, and that because of the folding the monomer addition rate increases to $K_a' > K_a$. The nature of the bond is not changed, only the rate has increased. One case of such conformation-dependent catalysis occurs in the N-carboxyanhydride synthesis of polypeptides (29). The significant aspect of this simple conformation-dependent, rate-controlled reaction is that the oldest exposed monomer in a helical chain is controlling the rate of addition of the next monomer. This amounts to a delay in the control mechanism corresponding to one turn in the helix. Now this delayed control process may not appear to have much evolutionary potential. However, we shall show how natural modifications of such conformation-dependent specific catalytic effects may produce elaborate hereditary coding in simple copolymers.

Next consider a copolymer growth in which the initial comonomer addition rates are K_a and K_b. Suppose that this chain also folds into a helix with five monomers per turn and that in this configuration the proximity of the $(n-4)^{th}$ to the $(n+1)^{st}$ position catalyzes the next addition step as in the previous example. However, now when we are using two types of monomer it is generally unlikely that the catalytic effect of the $(n-4)^{th}$ position is independent of the type of monomer at that position. If we now assume that there is a very strong rate-controlling effect of only the $(n-4)^{th}$ monomer on the addition of the next monomer, there will then be four possible control schemes or codes as shown in Table 1.

TABLE 1

Code	Monomer Type In $(n-4)^{th}$ Position	Catalyzed Monomer Type In $(n+1)^{st}$ Position
1.	a	a
	b	b
2.	a	b
	b	a
3.	a	a
	b	a
4.	a	b
	b	b

What will be the effect of these possible codes on the sequences in the copolymer chain? The last two codes will clearly degenerate into simple homopolymers no matter what the starting sequence may be. However, the first two codes will lead, respectively, to eight and four species of periodic copolymer. It is also clear that the linear sequence in each of these species is completely determined for a given code of Table 1 by any five adjacent monomers in a helical turn; and therefore, each turn of the helix can be considered as a genetic sequence. For example, if an a or a b monomer at the $(n-4)^{th}$ position increases the relative rate of addition of the same type of monomer as shown in the first code of Table 1, then any of the five cyclic permutation sequences, ababa, babaa, abaab, baaba, and aabab are equivalent genetic sequences for one of the species. The other seven species are generated from the two homopolymers, aaaaa and bbbbb, and the sequences, babab, aabaa, bbaba, baaab, and abbba or one of their cyclic permutations. It is important to realize that the specificity or relative catalytic power of the $(n-4)^{th}$ monomer, or in other words, the reliability of the tactic catalyst with respect to the types of added monomer will determine the inherent rate of mutation in this type of hereditary propagation. Of course, the addition of an uncatalyzed monomer, that is, the addition of a noncoded monomer, will not necessarily lead to a new species since all cyclic permutations of the end-turn sequence are genetically redundant. This would correspond to a mutation in DNA which still codes for the same amino acid.

Suppose now that we wish to increase the reliability of such a coding process. In other words we wish to increase the specificity and corresponding catalytic power for the addition of particular monomers. One reasonable mechanism for accomplishing this is to assume that more monomers must play a role at the active site, or in other words, that there are more interactions with the monomer which is to be added. Using the same basic model of a helical copolymer, suppose that not only the $(n-4)^{th}$ position monomer determines the type of addition but that the last monomer or n^{th} position also influences the specificy. This is sterically reasonable since the n^{th} and the $(n-4)^{th}$ monomer form a step dislocation in the helix at the position where the next monomer will be added. But now instead of only four possible coding schemes as

shown in Table 1, there are sixteen possible codes, again assuming only absolute specificity or so-called eutactic control. If we choose the code which catalyzes the addition of an a-type monomer when the n^{th} and $(n-4)^{th}$ monomer are the same type and a b-type monomer when the n^{th} and $(n-4)^{th}$ monomer are a different type, we will obtain four species of copolymer which may be represented by the four periodic sequences given below.

$$S_1: \ (a)_n$$

$$S_2: \ (bba)_n$$

$$S_3: \ (bbbaaba)_n$$

$$S_4: \ (bbbbbababaabbaaabaaaa)_n$$

The molecules within each species S_2, S_3, and S_4 will differ from each other only in the phase of the starting sequence. The sum of the length of all periods is $2^5 = 32$; and therefore no other eutactic species are possible for this given conformation and code. Of course we may also specify each species by five consecutive monomers from any part of each chain. For example, S_1 : aaaaa, S_2 : abbab, S_3 : baaba, S_4 : bbbbb. It is clear that species S_2, S_3 and S_4 have two, six and twenty other equally good starting genetic pentamer sequences, respectively.

If one forms a state-transition matrix for this polymer growth process listing all thirty-two initial and final states, the hereditary property will be apparent by the reducibility of this matrix into four sub-matrices corresponding to the four species of the chain. From this state-transition matrix description it will be obvious that the growth space for a given initial five-monomer chain is less than the physically possible state space for the five-monomer chains. The mechanism for this growth process, which we have not specified here, is therefore equivalent to a non-holonomic constraint.

Of course these simplified copolymer models are only to illustrate in the simplest way how true hereditary processes can arise at the molecular level. It is unlikely that tactic polypeptide growth would occur under so few constraints or in this particular autonomous form.

The optimum conditions under which such tactic catalytic growth of polypeptides might be found on the sterile primitive earth need further discussion (30). It is plausible from the known tactic processes in present cells, and the assumption of continutiy in evolution, that the most primitive polypeptide tactic catalysis also involved polynucleotides and the constraints of particle or membrane-like surfaces. The origin of the nucleotide-amino acid code remains a deep mystery, but from what we have said, the answer should not be expected in template models or non-catalytic processes.

XIV. The Reliability of Copolymer Catalysts

Even though we are not able to propose at present any detailed quantum mechanical mechanism for this type of conformation-dependent catalytic process, it is instructive to look for specific properties of such single copolymer hereditary catalysts which affect their reliability since this property is essential for evolution. The significant characteristic of enzyme catalysis is that the specificity may be controlled only by weak bond interaction whereas the catalysis or rate control operates only on the strong covalent bonds of the substrate. By contrast, classical machines, like clocks, use the strong bonded structures, such as the gears and escapements, to control the formation of weak bonds, that is, the frictional contacts between escapement pins and gear teeth. At the copolymer level a distinction between strong and weak bonds is already implicit in the concepts of monomer sequence and conformation since neither of these terms could be usefully defined if only one type of bond strength existed between monomers. The linear sequence is in fact defined as the monomer order obtained by following the strong bonds from one end of the chain to the other, while the conformation in linear chains refers to the shapes held by the weak bonds as allowed by the rotation or flexibility of the strong bonds, but not by breaking strong bonds. Of course in enzymes there are covalent bonds cross-linking the chain, but the definition of a linear sequence is still recognized by the most stable strong bond path.

What is the effect of these different roles of strong and weak bond interactions on the reliability of hereditary propagation in classical and quantum mechanical systems? We have already pointed out, following Schrödinger, that the covalent bond in a copolymer chain provides an ideal static storage mechanism for hereditary information. However, it is no less important that all dynamic hereditary transmission processes, which include replication, transcription and coding, operate with high reliability in the face of external and internal perturbations. In particular, it is more important that hereditary propagation cease altogether rather than propagate errors or lose the coding rules. Otherwise such uncontrolled catalytic activity only speeds up the destruction of the hereditary information. For example, in the helical copolymer model in which the helical structure is maintained only by weak bonds and the genetic memory by strong bonds, we could expect some form of error prevention upon heating since the helix will become a random coil first and thereby stop catalyzing monomer addition. On the other hand, in most classical machines, such as clocks, it is more likely that upon gradual raising of the temperature the machine will begin to operate with errors before it stops altogether. In other words, unless special error-correcting devices are employed, a classical clock will tell the wrong time before it melts whereas an enzyme will melt (denature) before it catalyzes the wrong reaction. For these reasons, we may expect optimum reliability and, therefore, survival value in hereditary systems in which the non-holonomic constraints representing the translation code mechanism are formed from weak-bonded structures, while the memory storage as well as the phenotypic expression of this description is preserved in strong-bonded metastable structures. Evidence of thermally-inactivated specific catalysts should therefore be assigned high significance in abiogenic experiments.

However, even under optimum operating conditions there remains a certain level of random thermal disturbance which affects the speed and accuracy of any classical measuring device. Normally when brownian motion or particle statistical fluctuations disturb the accuracy of a measurement, the only remedy is to increase the mass of the device or increase the time of observation so as to average out the fluctuations. Consequently high accuracy or precision in classical machines is incompatible with both

small size and high rates of operation. We are left then with the challenging problem of interpreting the enormous speed and precision of individual enzyme molecules without being able to use the statistics of the large numbers of degrees of freedom which we associate with macroscopic objects.

At first sight such speed and accuracy in single quantum mechanical systems may appear even more difficult to explain because of the uncertainty principle. For example, we may say that if we choose to measure the energy of a system with an accuracy of ΔE , then the measurement interaction must extend over a time interval of $\Delta t \geq \hbar/\Delta E$, so that speed and accuracy in this case are fundamentally incompatible. However, a more precise description of what enzymes actually accomplish does not involve such a simple relation between conjugate variables involved in the measurements. The specificity of enzymes appears to depend on the accurate fitting of a part of the substrate to a part of the enzyme. This implies that specificity depends on the measurement of relative position coordinates of certain regions of the substrate. But since the bond which is catalyzed may be at a different location, the momentum coordinates conjugate to the coordinates determining the specificity need have no direct relation to the speed of catalysis. On the other hand, if the enzyme structure has non-holonomic properties, which we claim is necessary for hereditary transmission, this implies that dynamic correlations must exist between the measured coordinates determining specificity and the momentum coordinates involved in the catalysis. The reliability of substrate recognition and the speed of catalysis now become a problem of describing how such dynamical correlations can be maintained without invoking classical structures. As we indicated in Section XI this is a difficult conceptual and mathematical problem.

Such reliability consideration will probably be crucially related to the size of enzymes and the structures associated with hereditary transmission, which of course includes the machinery for DNA replication and transcription as well as coding. It has been shown that the allowable accuracy of quantum mechanical measurements increases with the size of the measuring device, so that only in the classical limit can these measurements

be described as exact (31). This inaccuracy cannot be interpreted as the normal errors of measurement, or associated with the uncertainty of measuring a pair of non-commuting variables. Rather, it is the result of the attempt to describe the measurement transformation by the quantum equations of motion. Although quantitative estimates of reliability have not been made, it is plausible that copolymers must have grown spontaneously to a certain size before they could perform tactic catalysis with sufficient reliability to assure some evolutionary success. Perhaps such reliability requires membrane- or particle-bound copolymers as found in the tactic reactions in present cells.

The main point of this discussion is to emphasize the necessity of reliable molecular coding for any persistent hereditary evolution. There are two aspects to this necessity: first, the logical threshold as illustrated by von Neumann (see Sec. VI) which distinguishes the description or genotype from the construction or phenotype; and second, the physical reliability threshold which maintains the hereditary dynamics so that the rate of accumulation of information by natural selection can exceed the rate of error in the overall hereditary transmission process. These discussions suggest that neither template copying processes or non-specific catalysis can account for the origin of life. Even though classical automata may be designed by man to satisfy the logical and reliability thresholds useful for a kind of hereditary evolution, we would expect that quantum mechanical description will turn out to be essential for any fundamental understanding of living matter (32). Furthermore, the difficulties in quantum mechanical description of reliable hereditary processes do not appear to be simply a matter of complexity, but are likely to involve some of the most difficult conceptual problems which lie at the basis of physical theory. Would it be so surprising, after all, if the secret of life turned out to be based on something more than simple chemical description?

XV. Some Broader Questions

I have used the origin of life context in discussing coding and reliability because this level allows the simplest possible conception

of a molecular hereditary transmission process. We have seen that even at this level the theoretical difficulties remain serious. Nevertheless I believe that the concepts of coding and reliability will not only be useful, but also crucial at all levels of biological organization - cellular, developmental, evolutionary, and certainly in the higher nervous activity associated with the brain. We have used code to mean the relation between an elementary genotype and a phenotype, that is, a relation between a physical symbolic description and the physical object which is actually constructed from this symbolic description.

The process of cellular replication and in particular the development of the organism may be interpreted as an entire system construction process which requires a coding mechanism which interprets as well as replicates a description. Largely from studying the logic of abstract automata we may begin to appreciate how, through the discovery of simple codes, it is possible to generate elaborate ordered structure from relatively concise descriptions. Such a description-code-construction process cannot be adequately characterized as either preformation or epigenesis since, on the one hand, the construction may be totally unlike its description, whereas, on the other hand, the description and code structure together provide a complete, autonomous generation of the phenotypic construction within the crucial limits of reliability.

At the evolutionary level this concept of a symbolic genetic description and its code structures must be broadened to a larger system which includes not only the description of the system itself but also a description or a "theory" of the environment. In the evolutionary context the phenotype itself now plays the role of a composite measuring device which tests the descriptive theory through its interactions with the real environment. In this language we must also expand the concept of reliability to include the overall predictive value of this description-code or theory-measurement system. I believe it is then reasonable to associate this overall predictive value with what is called the "measure of fitness" in evolutionary theory.

Finally, at the level of nervous activity in the processes of memory and intellectual theory making, we are again searching for more elegant code structures which allow the maximum predictive reliability over the

widest domain, but which can be generated from relatively short symbolic descriptions. Perhaps we could even say that the characteristic sign of biological activity at all levels is the existence of efficient and reliable codes. However, at none of these levels can we evade the basic question of how biological systems achieve the unique reliability of their codes through which they have so clearly distinguished themselves from nonliving matter. Even at the level of memory and consciousness it is possible that single enzymes may provide the crucial transmission links or codes from the senses to the internal descriptions in the brain.

XVI. Summary

We have asked once again the historical question: Are the characteristic processes of biological organisms understandable in terms of the basic laws of physics? I have tried to show that in spite of the many classical models of cellular structures and functions there are severe difficulties in accounting for the reliability of hereditary transmission in terms of the elementary laws of physics. I have proposed that the ultimate source of the unique distinction between living and nonliving matter does not rest on idealized classical models of macromolecules, template replication, or metabolic control, but on the quantitative reliability of molecular codes which can correlate the contents of a quantum mechanical description with its classical phenotypic expression. To understand such a correlation between quantum descriptions and the corresponding observable classical event requires a quantum theory of *measurement* applied to elementary molecular hereditary processes. Such a theory presents serious, though I hope not insurmountable, conceptual and formal difficulties for the physicist. However, in spite of the unsolved theoretical questions we can specify certain necessary conditions for individual molecular coding structures. These conditions suggest that the seat of coding or measurement processes in living matter is the individual non-holonomic enzyme catalyst, although it is likely that other structures in the cell serve to increase the reliability of these codes.

Broadly interpreted, the existence of a molecular code of exceptional reliability is essential not only for the origin of life, but also for the development of the individual, the evolutionary process of natural selection and survival of hereditary traits, and even the symbolic coded descriptions which we call intellectual theories. But whatever level of complexity we study, we may expect to find the conformation-dependent, tactic catalyst serving as the most elementary hereditary transmission device. For these reasons, I believe that describing such reliable hereditary molecular events in terms of quantum mechanics remains the fundamental problem which we must study, not only for theoretical biology, but perhaps also for a firmer epistemological basis for physical theory itself.

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2. An example of such a statement is found in J. D. Watson, The Molecular Biology of the Gene, W. A. Benjamin, New York, 1965, p. 67: "Until recently, heredity has always seemed the most mysterious of life's characteristics. The current realization that the structure of DNA already allows us to understand practically all its fundamental features at the molecular level is thus most significant. We see not only that the laws of chemistry are sufficient for understanding protein structure, but also that they are consistent with all known hereditary phenomena".

   A much earlier, pre-DNA optimism toward heredity was expressed by Thomas Hunt Morgan in 1919: "That the fundamental aspects of heredity should have turned out to be so extraordinarily simple supports us in the hope that nature may, after all, be entirely approachable". (Quoted from F. H. C. Crick, On Molecules and Men, University of Washington Press, Seattle, 1966.)

3. E.g., from D. C. Phillips, The Three-dimensional Structure of an Enzyme Molecule, Scientific American 215, 90 (1966): "... as a result of all the work now in progress we can be sure that the activity of Fleming's lysozyme will soon be fully understood. Best of all, it is clear that methods now exist for uncovering the secrets of enzyme action".

4. E.g., from J. C. Kendrew, Scientific American 216, No. 3, 142 (1967) (reviewing Phage and the Origins of Molecular Biology, J. Cairns, G. Stent, and J. Watson, eds.): "... up to the present time conventional, normal laws of physics and chemistry have been sufficient, and at least in the opinion of this reviewer the forward horizon is clear of awkward facts that will require new or paranormal laws for their explanation.".

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13. ABSTRACT

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