LES CAHIERS DE L'INSTITUT DE LA VIE

1967 No 12

LES
CAHIERS
DE L'INSTITUT
DE LA VIE

Siège: 89, Bd Saint Michel, Paris Ve
Téléphone: 033-94-86
Périodicité: trimestrielle

Prix du numéro: France 5 F. Étranger 6 F
Abonnement: France 18 F. Étranger 22 F
Conditions spéciales aux membres de l'Institut de la Vie.
Renseignements au Siège.

SOMMAIRE

CONFÉRENCE INTERNATIONALE
PHYSIQUE THÉORIQUE ET BIOLOGIE
Versailles 26-30 juin 1967 pages

Journée du 26 juin 1967, 2ème séance

Journée du 26 juin 1967

CONCEPTS THEORIQUES

2ème séance

PRÉSIDENT S. L. SOBOLEV

J. D. COWAN

Some Remarks on Neurocybernetics

W. M. ELSASSER

What is Theoretical Biology?

General discussions

Theoretical Physics and Biology, © 1969, *North-Holland Publ. Co., Amsterdam*

SOME REMARKS ON NEUROCYBERNETICS

JACK D. COWAN

Committee on Mathematical Biology, The University of Chicago, U.S.A.

The last quarter of a century has seen the emergence and development of cybernetics, the science of information and control. As a result, a new language has evolved out of the continued efforts of scientists and engineers to make precise such concepts as "communication channel", "automaton", and "control system". This language has been widely used in those sciences which have to deal with the interaction of animals and machines with their environments. One science that has drawn heavily on this language is neurology. Cybernetic concepts have been used in many different ways to investigate how the brains of men and animals might work.

Perhaps the earliest example of the use of this language in neurology is to be found in the 1943 publication by W. S. McCulloch and W. H. Pitts of "A logical calculus of the ideas immanent in nervous activity" [1]. In this paper, the concept "formal neuron" was introduced, essentially an abstraction from then current details of neuronal operation. These formal neurons operated upon and emitted, at specified times, binary "all-or-none" signals. Their junctions, called "synapses", were either excitatory or else totally inhibitory. They functioned by computing the algebraic sum of the values of their inputs, 1 and 0, subsequently emitting an output signal if, and only if, this sum exceeded a certain specified threshold. Formal neurons could be made to represent the elementary operations of two-valued logic, and *a fortiori*, formal neuronal networks to represent complicated logical formulas [2]. To the extend to which the concept "formal neuronal network" symbolizes the process whereby brains respond to and represent stimuli, the McGulloch–Pitts theory is similar to that of K. J. Craik's [3] regarding the nature and function of neuronal networks. A corollary of the McCulloch–Pitts theorem is also of interest: formal neuronal networks plus "receptors" and "effectors" are equivalent to Turing machines. A Turing [4] machine is itself a formalization of, and an abstraction from, the processes underlying computing. The equivalence of the two concepts, therefore, led immediately to the idea that in at least some aspects of signal processing, brains and computers are similar. N. Wiener, in his now classic book "Cybernetics" [5] developed this analogy, incorporating chapters on computing machines and the nervous system, on gestalts and universals and on cybernetics and psychopathology.

This research was sponsored in part by the Physics Branch, Office of Naval Research, Washington D.C., under Contract No. F61052 67C 0061.

Any direct analogy between formal neuronal networks and brains requires the existence in brains of specific circuits, so that there has to be a process of selection of nerve-cells and of the pattern of interconnection, the anatomy or the "wiring-diagram", and a rejection of all other possibilities. However, ablation studies on the brains of many animals [6] apparently indicated that such complex signal processing tasks as visual integration were independent of the specific details of the wiring diagrams of the visual cortex. Even extensive destruction of this tissue did not produce marked disintegration of function, although those activities that persisted were somewhat retrenched. This suggested that perhaps the circuits were redundant throughout areas of nervous tissue and that only gross parameters of the tissue such as the mean number of cells and their interconnections were reliable measures of the tissues' functioning. Wiener [5] suggested that nervous tissue might be similar to large telephone exchanges in containing redundant cells and interconnections, and that messages might be simultaneously transmitted from area to area along many distinct pathways, and might be repeated several times along each pathway, the final decision concerning the validity of signals reaching any area of nervous tissue being determined by some kind of voting procedure. J. von Neumann [7] in the paper, "Probabilistic logics and the synthesis of reliable organisms from unreliable components" gave the first proof of the existence of designs for the construction of neuronal networks which might survive extensive malfunctions of components, or failures of individual formal neurons and of errors in and damage to their connections. Von Neumann's designs utilized the replication of many individual circuits, the simultaneous transmission of messages by many circuits, and "majority-voting" circuits to ensure the overall reliability of signal processing and transmission. Von Neumann was not satisfied with the results. He considered his treatment of error to be rather *ad hoc*, and he suggested that error should be the subject of a thermodynamical theory, as C. E. Shannon had treated the concept of information [8]. He was also aware that formal neuronal networks were digital in their mode of operation, whereas those comprising brains were not, despite their use of pulses in some operating modes [9].

S. Winograd and the author applied Shannon's theorem concerning the reliable transmission of messages through a noisy communication channel to include computation, and so provided part of von Neumann's suggested thermodynamical theory of error for formal neuronal networks [10]. The resulting design for the construction of formal neuronal networks that function correctly in spite of malfunctions of individual neurons, or of errors in and of damage to wiring diagrams, differs in interesting ways from von Neumann's. The ability of formal neuronal networks to function correctly in spite of viccissitudes depends on their composition by anastomotically redundant circuits. In von Neumann's prospectus, this kind of redundancy was sought by incorporating many copies of the one and only one circuit necessary for the representation of the specified functions which

are intended to determine the behaviour of the network. In the Winograd–Cowan theory, however, the redundancy is obtained, not by multiplication of identical circuits, but by replacing the specified functions by a greater variety of more complicated functions which require circuits containing many more and richer formal neurons and interconnections than the circuits required for the original specified functions. The key to theory is that the rules governing this replacement constitute error-correcting codes (*see* [11]). The network that results from such an encoding is immuné to many kinds of error, i.e., it is largely "error-insensitive". The degree of error-insensitivity obtained depends upon the complexity of the requisite behaviour, on the frequency of errors, and on the level of redundancy introduced by whatever code is used. Because the code operates on functions and not on circuits, the redundancy obtained is functional, i.e., more functions are represented in the encoded network than in its precursor. Because of the nature of error-correcting codes, any one specified function appears in many of these encoded functions, and any one encoded function is essentially a different mixture of many of the specified functions. It is the multiple representation of a multiplicity of specified functions which leads to error-insensitive operation, rather than the mere replication of circuits. In short, it is the diversity of the encoded function that is computed by each individual formal neuron comprising the encoded network which leads to the efficiency of design. So the number of formal neurons required to realize any given mode of behaviour at some level of error-insensitivity, despite probability of malfunction of individual formal neurons and of error in the wiring, is ultimately as small as Shannon's theorem indicates is possible. Naturally, the formal neurons required to represent encoded functions are much more complicated than those which would be required to represent only the original specified functions. The application of Shannon's theorem thus requires that the more complicated formal neurons be no less reliable than the simpler ones, a requirement which is equivalent to assuming that the extra "hardware" required for coding is completely error-insensitive, as in Shannon's theorem. The Winograd–Cowan theorem is, in fact, like von Neumann's theorem, an existence theorem; but it differs from it in requiring a minimal number of very complicated circuits and formal neurons rather than a large number of simple circuits of threshold formal neurons. Our theory is the other extreme to von Neumann's theory wherein complication is minimized at the cost of increased replication, in that redundancy is minimized at the cost of increased complication, to attain some requisite level of error-insensitivity. Suitable combinations of the two techniques, functional coding followed by the replication of the resulting circuits, plus a randomization of the interconnections between them, lead to efficient and practical error-insensitive networks.

However, these networks can persist only for lifetimes that are limited by the error and failure rates of their components. There is an ageing effect, so that the reliability of function of these networks degrades under the cumulating effects

of uncorrected failures. W. H. Pierce [12] has shown how "adaptive" networks may be designed whose lifetimes are substantially longer than those of the above networks. A basic defect of the techniques outlined, in which majority voting effectively controls errors, is that, since those inputs to a given formal neuron which issue from a failed one will be permanently in error, a consistently reliable minority may be outvoted by a consistently unreliable majority. Such a limitation may be overcome by using more complicated formal neurons whose inputs are weighted according to their reliabilities. This requires computation by the recipient formal neuron of these reliabilities. Pierce has proved that such computations can be carried out. If input errors are statistically independent, the input weights α_i can be selected so that the output of the formal neuron is the digit most likely to be correct, on the assumption that what is required of the formal neuron is the representation of the majority function [13]. One variant of this is particularly interesting. In this, if p_i is the number of coincidences and q_i the number of disagreements between the ith input to, and the output from a given formal neuron in a cycle of m operations, then the selections $\alpha_i = \log(p_i/q_i)$ lead to the computation of the most likely estimate of the reliabilities of the inputs for the representation of the majority function.

There are evidently good grounds for asserting that reliable networks of competent formal neurons can be constructed, using the techniques of functional coding followed by replication of the resulting circuits, together with feedback controlled selection of vote-weights, which would be efficient and long-lasting compared with their components. However, the question remains of how such networks are to be constructed. The existence of specific circuits in a network requires the selection of components and wirings. For these redundant networks the problem is crucial; i.e., the amount of selective information required to specify them is very large. Not only do the wirings and thresholds have to be specified, but also particular patterns of synaptic interactions. Vote weights do not have to be selected because the process is automatic, but the necessary wirings of formal neurons need to be more complicated than those of non-adaptive networks. Thus, a very complicated programme is required for the construction of these networks, that contains all the requisite information. An important and interesting question concerns the possibility of leaving the bulk of the selection process to be performed during the lifetime of the network, i.e., by adaptation. A. M. Uttley [14] has outlined how certain replicated circuits might arise by chance in a randomly interconnected network, thus diminishing the amount of selective information what has to be supplied either "genetically" or "epigenetically". What remains is the problem of specifying the complicated functions required for functional coding. For high levels of functional coding, each formal neuron need only represent a random selection of the specified functions of the network, provided it correctly decodes its inputs. It is interesting that recent work on the design of adaptive machines capable of learning to classify, represent,

and recognize patterns of stimuli, has given rise to machines whose functional organization is apparently very similar to the redundant networks we have designed. [*See* 15, 16].

The combination of such theories of automata and information-processing with what might be called machine theories of adaptation, provides a not unreasonable model of what might be the organization of those parts of brains concerned with perception, learning, and perhaps with memory. We have cited Lashley's work on ablation effects. Lashley concluded that it was not possible to demonstrate the isolated localization of the memory trace or "engram" anywhere within the nervous system. He supposed that there was no special reservoir of cells which would serve as the seat of special memories, every instance of recall requiring the activity of millions of neurons. Moreover, the same neurons which retained the engram must also participate in countless other activities. [*See* also 17 and 18]. Sperry has suggested a number of principles that might give rise to this property: multiple interconnections between nerve-cells, the fidelity of the wiring being controlled by specific biochemical factors, much overlapping of interconnections; multiple reinforcement of any given function from numerous different sources any one of which may itself be capable of sustaining the activity; reciprocal and surround inhibition between and among neurons; the arrangement of cortical circuits in vertical, rather than horizontal, dimensions and the bilateral duplication of the cerebral hemispheres. J. C. Eccles [19] and A. E. Fessard [20] have inferred from their own experimental studies that presynaptic and lateral inhibition between and among neurons are important features contributing to error-insensitivity. In considering changes in the "evoked potentials" in various areas of the brain, associated with the engramming of conditioned responses, E. R. John [21] demonstrated an effect related to the replication of circuits and the delocalization of function which we have discussed, namely that evoked potentials following the engramming have similar shapes, even over many anatomically distinct regions of the brain.

In the light of these experiments we note certain logical requirements on the structure of the error-insensitive networks obtained by functional coding techniques. These are the existence of large numbers of both excitatory and inhibitory synapses at all units, the existence of many presynaptic "axo-axonal" interconnections, a great deal of multiple interconnection and overlap, and the existence of lateral inhibition between groups of neurons. Furthermore, as a consequence of functional coding, there is an extensive representational system in these networks, any unit of which can be activated by many different patterns. Finally, the reliable activation of any complete pattern of activity would require the synergic activity of many units. All these features of functionally coded networks appear to have experimental correlates, most of which are the result of experiments performed on the central nervous system proper. We should not expect to find high levels of functional coding in peripheral areas, but rather many replicated

circuits more in line with the "telephone-exchange" analogy. At some intermediate stage where the degree of synaptic interaction among neurons is sufficiently high to sustain functional coding as well as circuit replication there will emerge assemblies of synergic neurons, which may be taken to be the "functional units" of the network. Perhaps the vertically organized groups of neurons found in sensory projection areas [22, 23] may be taken to be the experimental correlates of these functional units.

We consider it to be of some importance that deductive models of the organization of neuronal networks be forthcoming which lead to the specification of such entities as functional unit, engram, and so on. R. L. Gregory [24] has made the point that a knowledge of function is required to classify observed biological features into "essential" or "accidental" properties, and that it is only when the functional units of the system being studied can be identified, that deductive inference and not mere description becomes possible. Gregory made the further point that the neurologist is never able to identify functional units directly by observing neurons and their interconnections; in all cases, knowledge is needed of what neurons do, and of how they do it. This raises a peculiar and difficult problem common to almost all attempts to apply cybernetics to biology. For, in order to do this, one must know precisely what is the ensemble of possibilities upon which operates the selection process that alone gives meaning and utility to the ideas of message and information. For the neurological problem, this is equivalent to saying that one needs to know the code, or codes, of the nervous system. Thus, any real application of theories of formal neuronal networks can follow only from a knowledge of what neurons do and of how they do it. This takes us far from the ablation experiments of the physiological psychologist, to the electrophysiologists who measure not behaviour deficits and the like, but the firing patterns of neurons and the changing electrical potentials of nervous tissue, the ECoG and EEG.

Once we enter the domain of experimental neurophysiology, however, it becomes difficult to see how the automata models apply to data.

It is clear that the automata approach is seriously deficient in many respects. In the automata, we have considered changes in the firing patterns occur only at instants specified by an external clock, i.e., they are already "synchronized" in the time domain. There is no clear evidence that the CNS operates in such a fashion. In any case, the formal neuron is a rather crude abstraction of neuronal behaviour, and the theory covers special aspects such as functional stability and does not serve to help us understand the responses of nets comprising many thousands or many millions of cells. The theory, in fact, was designed for the analysis of small-scale local interactions between abstract functional units. Digital computer simulations of neuronal nets [26, 27] together with some combinatorial analysis [27, 28] have given us some indication of the type of activity to be found in homogeneous networks of randomly interconnected formal neurons. If there

are only excitatory synapses in the net, the only stable states of activity are either a large proportion of all the units in the net are active, or else the net is quiescent. This is the "switching effect", discovered by many workers. It has been suggested that a neuronal network which acts itself as a switch might serve as a functional unit, and so correspond to one of McCulloch and Pitts' formal neurons. In case there are also inhibitory synapses, the behaviour is more complex and several intermediate stable levels of activity can persist. Farley has shown that even small networks comprising about one hundred cells can exhibit quite complicated behaviour, recruiting responses, augmenting responses, rhythms and so on, that are reminiscent of experimental phenomena. What is lacking in this approach, however, are the concepts and mathematical tools that would further the analysis of the responses of very large networks, nor is there any real attempt to face the problems of coding in these networks.

There has been one interesting attempt at a mathematical treatment of the responses of large nets [29]. In this, neurons are assumed to be randomly distributed in a mass with a given volume density. The neurons have thresholds, synaptic delays, EPSPs and IPSPs, and a summation time constant. Attention is directed to the proportion of cells becoming "sensitive" per unit time. Sensitive cells are those which are not refractory and can, therefore, be fired by a sufficiently potent stimulus. Although the mathematical treatment is not rigorous, the conclusions are essentially correct. The switching effect is discovered, and the conditions for the distortion-free propogation of plane waves of neuronal excitation are given. It is shown that the connection function which gives such propogation is equivalent to that one found empirically by D. A. Sholl [30]. Since only excitatory synapses are present, this wave propogation is unstable and depends critically on the stimulus, on the cell properties, and on the local density of interconnections. Beurle introduced two mechanisms of interest. Waves were stabilized by "servo" control from external nets which acted by firing off cells ahead of the wavefronts. And cell thresholds were assumed to be dependent upon past activity. These extensions of the random network assumptions are important. The servo idea is an attempt to treat network interactions, the control of one network by another. Threshold modification by past activity changes the responses of a network, according to past responses. So the network can be trained, given the proper feedbacks, to act as a permanent store of messages. Indeed, all the possibilities of behaviour, functional stability, adaptation, and so on, which we considered to be present in functionally stable automata, are to be found in these networks. However, the scale has been changed, so to speak, in that complete networks play the role of functional units, and dynamical variables play an important role in the encoding of stimuli.

There is, therefore, the intriguing possibility that some kind of answers to the problems of modelling some aspects of the activity of neuronal networks in the CNS might be forthcoming from a mathematical formulation closely related to

Beurle's. But there are a number of problems that must be solved before this approach can be made useful. The analysis has some defects. For example, the effects of refractoriness, of the finite size of the network, and of delays, are not properly formulated. To some extent, these defects are not too serious. Correct formulations of similar problems have been given by J. S. Griffith [31] and by M. ten Hoopen [32]. Their conclusions are similar to Beurle's concerning switching and stability, if somewhat less far-reaching in scope. However, what is really lacking from the whole approach is that it does not make contact with the experimental variables of the neurophysiologist, the histograms, correlograms, ECoGs and so forth, and so, in this sense, it is not a testable model for the responses of neuronal network in the central nervous system. Moreover, while the image of interacting waves of neuronal excitation suggests many possibilities for the coding of messages, it has not been used so far to produce precise, quantitative predictions of how and where permanent changes take place in the networks of the central nervous system, and what they represent.

What is required, then, is a novel mathematical formulation of the responses of neuronal networks that takes account of many of the organizational features of the central nervous system that we have listed, in which the variables relate to measureable quantities by current experimental and data processing techniques, and in which there is a precise hypothesis concerning the nature of neuronal coding. It is not too much to hope that this theory will be forthcoming during the next decade.

Acknowledgement

The author would like to express his gratitude to Lord Jackson of Burnley, F.R.S., of the Electrical Engineering Department, Imperial College for the warm hospitality he has enjoyed there as an academic visitor while the above research was carried out; and to the Director of the National Physical Laboratory, Teddington, and the Superintendent of the Autonomics Division there, for making available to him valuable experimental and computing facilities, while he was there as a guest worker.

References

[1] W. S. McCulloch and W. H. Pitts, *Bull. Math. Biophys.* **5** (1943) 115–133.
[2] S. C. Kleene, *Automata Studies*, Eds. C. E. Shannon and J. McCarthy, (Princeton Un. Press, 1956) 1–42.
[3] K. J. W. Craik, *The Nature of Explanation*, (Cambridge Un. Press, 1943).
[4] A. M. Turing, *Proc. Lond. Math. Soc.*, **42**, 230 (1937) 137.
[5] N. Wiener, *Cybernetics*, (M.I.T. Press, 1948).
[6] K. S. Lashley, *Soc. Exp. Biol. Symposium* **4**, (Cambridge Un. Press, 1950).

[7] J. von Neumann, *Au'omata Studies*, loc. cit. [2] 43–89.
[8] C. E. Shannon, 1948 *Bell System Technical J.* **27** (1948) 379–423, 623–656.
[9] P. Elias, *Sensory Communication*, Ed. W. A. Rosenblith, (M.I.T. Press, 1961).
[10] S. Winograd and J. D. Cowan, *Reliable Computation in the Presence of Noise*, (M.I.T. Press, 1963).
[11] W. Peterson, *Error-Correcting Codes*, (M.I.T. Press, 1961).
[12] W. H. Pierce, *Redundancy Techniques in Computing Systems*, Eds. R. H. Wilcox and W. C. Mann, (Spartan Books, 1963) 229–250.
[13] E. F. Moore and C. E. Shannon (J. Franklin Institute, 1956).
[14] A. M. Uttley, *Information and Control* **1** (1959) 1–24; *Brain Research* **2** (1966) 21–50.
[15] W. K. Taylor, 1956 *Information Theory*, Ed. E. C. Cherry (Butterworth, 1956) 314–328.
[16] F. Rosenblatt, (1958) Cornell Aeronautical Labs., Report No. VG-1196-6-1, *Principles of Neurodynamics*, (Spartan Books, 1962).
[17] R. Sperry, *Principles of self Organization*, Eds. H. von Foerster and G. W. Zopf, Jr., (Pergamon, 1960).
[18] J. Z. Young, *A Model of the Brain*, (Oxford Un. Press, 1964).
[19] J. C. Eccles, *The Physiology of Synapses*, (Springer, 1964).
[20] A. E. Fessard, *Information Processing in the Nervous System*, Eds. R. W. Gerard and J. W. Duyff, (Excerpta Medica, 1964), 415–418.
[21] E. R. John, 1964, Ibid.
[22] V. B. Mountcastle, *J. Neurophysiol.* **20** (1957) 408–434.
[23] D. H. Hubel and T. N. Wiesel, *J. Physiol.* **160** (1962) 106–154; *J. Neurophysiol.* **28** (1965) 229–289.
[24] R. L. Gregory, *Mechanization of Thought Processes*, (H.M.S.O., 1959) 669–650.
[25] J. D. Cowan, *Encyclopaedia of Information, Linguistics and Control*, (Pergamon Press, 1967); *Automata Theory*, Ed. E. R. Caianiello, (Academic Press, 1964).
[26] B. G. Farley, *Computers in Biomedical Research* 2, (Academic Press, 1965).
[27] D. R. Smith and C. H. Davidson, *J. Assoc. Computing Machinery* **9** (1962) 268–279.
[28] J. S. Griffith, *Biophys. J.* **3** (1963) 299–308.
[29] R. L. Beurle, *Phil. Trans. Roy. Soc. London* **240** (1956) 669.
[30] D. A. Sholl, *Organization of the Cerebral Cortex*, (Methuen, 1956).
[31] J. S. Griffith, *Bull. Math. Biophys.* **25** (1963) 111–120; *Bull. Math. Biophys.* **27** (1965) 187–195.
[32] M. ten Hoopen, *Cybernetics of Neural Processes*, Ed. E. R. Caianiello, (C.N.D.R., 1965) Rome.

Theoretical Physics and Biology, © 1969, *North-Holland Publ. Co., Amsterdam*

WHAT IS THEORETICAL BIOLOGY?

WALTER M. ELSASSER

Department of Geology and Biology, Princeton, U.S.A.

One may trace the beginning of modern efforts in theoretical biology to a celebrated paper of Niels Bohr that appeared in 1933. I should say here at once that my personal interest in theoretical biology was largely aroused by this work. My basic ideas began to develop during my stay in Paris in 1934/35. I am therefore particularly grateful to the Organizing Committee of this Meeting for the opportunity to return to the places of my early stimulation and development.

Bohr's paper indicates how one can apply the ideas of quantum theory to biological problems. What quantum physics has taught us on a more philosophical level is that each progress in our understanding of the behavior of matter is achieved at the price of a corresponding loss: We are no longer able to trace in detail the geometrical arrangements and clearcut causal relationships that govern motions in classical physics. It is a familiar fact that the concept of well-defined orbits of particles ceases to exist in quantum theory. Instead, one has a statistical theory in which prediction is profoundly limited. In theoretical biology, analogous arguments hold but they apply now to a higher level of organization.

This raises at once the question whether changes are required in the mathematical apparatus of quantum mechanics. Our answer is that such changes are unnecessary. Organisms differ from other bodies by their extraordinary complexity. Their dynamics, however, takes place at the energetic levels of ordinary chemical reactions. There are no plausible grounds for changing the laws of physics solely because of an increase in complexity. What then is the new element which appears in the analysis of living systems? We claim that this novelty lies precisely in complexity itself.

On combining the uncertainty relations with this complexity, Bohr concluded that the perturbations which result from quantum measurements are of fundamental importance in biology. Such measuring processes interfere with the delicate operation of a system of as complex a design as an organism. In order to gain a thorough knowledge of the system, which is indispensable for precise prediction, the measurements must be so thorough as to disturb the organism seriously; eventually the animal will become sick and die. But on the other hand, in the absence of prediction science ceases to be analytical and remains on a purely descriptive level.

In my own writings I have emphasized that predictions may be derived from two different procedures. One of these is the determination of initial values,

as already mentioned. The other may be called the method of the sampling of classes. One can for instance predict the behavior of some variety of molecules by measuring other molecules of the same kind, notwithstanding the fact that the measured molecules may be destroyed in the process. This is of course a common method in physics and chemistry. I have been able to show that the application of this method to the classes of biology, e.g., species, leads also to fundamental limitations of prediction. These limitations arise from the fact that organisms of the same class differ from each other in very numerous particulars by virtue of the pervasive inhomogeneity of all living matter.

The totality of these limitations imposed on prediction corresponds to what may properly be called the semi-autonomous character of living matter. If we had chosen to apply a similar terminology in quantum theory, we could have said that the stability of atoms and molecules is a semi-autonomous phenomenon, in the sense that an explanation of this stability in terms of classical physics is not possible. In a similar fashion the stability of organisms and even more the tremendous precision of developmental processes are properties which cannot be fully explained by means of ordinary physics. Undoubtedly, a great part of this stability can be explained in mechanistic terms, for instance by feedback devices. But owing to the intrinsic complexity of living matter one cannot make the purely physical mode of explanation an exhaustive one.

An important reservation is needed at once. This is that physics and chemistry are never false in the organism. They are incomplete. What is meant here is that the initial conditions can never be determined with the required accuracy; nor can one select a biological class whose members would be sufficiently similar to each other to allow adequate prediction based on the method of sampling. The primary distinguishing characteristic of living matter is, therefore, the essential complexity, inhomogeneity, and variability of this matter. We are thus able to define theoretical biology in the following manner: Theoretical biology is the science of radically inhomogeneous classes. Physics, on the other hand, is the science of homogeneous classes, if not a priori, then at least in fact and by usage.

In the course of my investigations I have become convinced that complexity, inhomogeneity, and variability are not only necessary conditions for the existence of life; they are also sufficient in a simple sense: Any proposition about life inasmuch as it deals with it as a semi-autonomous phenomenon must be based upon this inhomogeneity, beyond the purely physico-chemical properties of the system considered. Again, we may be confident that this is the only new principle required when we want to characterize life in a general and essentially abstract manner.

We can exhibit the same ideas in a different form, mostly to show their relationship with what is usually called molecular biology. We know that the organism possesses many well-defined constituent parts which one can synthesize in the laboratory; or else one will certainly be able to do so in the future. We shall

designate these as homogeneous components. They are primarily macromolecules. In the living organism, these homogeneous components are immersed into a radically inhomogeneous environment. This inhomogeneity of the internal environment arises out of the almost endless variation of geometrical relationships among parts, and out of the almost limitless variability of the low-energy chemical reactions which this entails. One may express this by saying that in the organism the dynamics of the homogeneous components needs must be coupled into the inhomogeneity of the internal environment.

In order to gain a better understanding of the implications one ought to compare inhomogeneity with what the physicist calls noise. Although noise is a statistical phenomenon, one presumes always that one can form averages over any variable whatsoever. I propose then to define an inhomogeneous class in the following manner: It is a set composed of a finite number of objects such that one can never obtain enough samples to give an operational significance to all averages that it may be possible to define from a purely mathematical standpoint. From this there results an essential limitation of prediction as compared to the case where homogeneous classes would be available.

Bohr had long ago proposed that every fundamental progress in our knowledge of the properties of matter is tied to a loss of so called explanation. This idea found its original application in quantum mechanics. Uncertainties of a quite analogous kind turn out to be basic in theoretical biology. The abstract apparatus which expresses these new uncertainties is the theory of inhomogeneous classes. One fact stands out: When we go from abstract models in the more conventional sense to a theory of abstract *classes* which are not necessarily homogeneous, we introduce a freedom and a generality which are not to be found in traditional theoretical science. I have convinced myself in the course of many years that we have in hand here the chief tool that is required in theoretical biology.

References

Walter M. Elsasser, *The Physical Foundation of Biology*, 219 pp. (Pergamon, 1958).

Walter M. Elsasser, *Atom and Organism*, A new Approach to Theoretical Biology, 143 pp. (Princeton Un. Press, 1966).

See also a forthcoming paper by the author in vol. 3 of the series *Towards a Theoretical Biology*, ed. by C. H. Waddington (Edinburgh Un. Press, 1969).

Theoretical Physics and Biology, © 1969, *North-Holland Publ., Amsterdam*

GENERAL DISCUSSIONS

A. LICHNEROWICZ: M. Grassé nous disait qu'il fallait trouver un langage commun: un premier thème est revenu, entre M. Prigogine et M. Fröhlich: l'expression "non linéaire". Je voudrais dire à la fois mon accord et les limitations qui me semblent s'imposer.

Il faut d'abord faire très attention, en parlant linéaire et non linéaire. Il s'agit de choses dans lesquelles le linéaire peut sécréter des êtres non linéaires et des effets non linéaires. Et par conséquent il faut dire exactement ce qui est, dans chaque cas, effectivement non linéaire. Mais enfin nous serons d'accord, je crois ... Et je pense que le mot "non linéaire", qui embrasse le linéaire, est une des clés de notre dialogue.

Secundo: je voudrais rendre hommage, en particulier, à l'effort d'arrachement à la thermo-quasi-statique, en faveur d'une vraie thermodynamique, fait par M. Prigogine; là est probablement l'un des modes d'approche de nos problèmes. C'est l'étude de régimes permanents stables. Et je voudrais peut-être poser, en même temps, à M. Prigogine, une question. Un certain nombre des choses qu'il a dites sont en exact parallèle avec certaines des méthodes contemporaines et anciennes de l'économie mathématique. Nous savons d'ailleurs qu'il y a des parallèles entre thermodynamique et economie. Et en economie les fonctions convexes jouent un rôle important pour les problèmes de stabilité (de stabilités un peu plus globales que les siennes). En fait, Monsieur Prigogine, votre condition du second ordre est une condition de convexité locale.

Je crois que l'introduction de symboles mathématiques du type fonctions convexes, pour certains problèmes, avec contraintes, doit jouer dans l'avenir un rôle important.

Tertio: je voudrais affirmer ma foi dans la biologie théorique, mais je ne crois pas qu'elle doive avoir, à ce stade, un instrument privilégié. Je pense que nous devons également avoir confiance en ce qui a été dit tout à l'heure, par exemple par M. Elsasser, qui est une approche très intéressante des classes hétérogènes aussi dans la *vraie* thermodynamique. Sous les réserves qu'il faut tout de même bien prévenir nos amis biologistes que le mot "entropie", qu'on met à toutes les sauces, n'est pas toujours parfaitement aussi clair et aussi mesurable que nous souhaiterions. Je pense que ces approches convergentes doivent être poursuivies distinctement, et que nous ne pouvons pas, en ce moment, espérer *une* seule approche.

Bien entendu, la mécanique quantique jouera son rôle. Pour le moment, elle est linéaire. Essentiellement en ce sens que ses équations fondamentales sont linéaires. Mais on sait que des essais sont faits pour sortir du linéaire. En gros,

j'ai l'impression que c'est la description qui s'applique aussi à M. Prigogine. Nous avons des équations, disons en gros, rigoureuses, non linéaires, comme équations fondamentales, dans beaucoup de situations; et nous étudions la stabilité à partir des équations aux variations qui forment le système linéaire canoniquement associé. C'est cela que nous faisons constamment, sous des formes et avec des discours, physiques ou chimiques, de type varié.

W. M. ELSASSER: Je suis tout à fait d'accord avec M. Lichnerowicz: j'ajoute l'idée que la théorie des classes hétérogènes joue un rôle similaire à l'usage qu'on fait de la géométrie riemanienne dans la cosmologie. Sans quoi, on aura la contradiction que Kant, le philosophe, constatait il y a deux cents ans: la contradiction entre le problème d'un univers infini et la possibilité de construire un univers sensible. Alors, avec l'introduction de la théorie des classes hétérogènes, des contradictions semblables, entre la nécessité et l'indéterminisme (c'est-à-dire la liberté et le potentiel créateur), . . . ces choses-là disparaissent. Mais naturellement, il faut aussi avoir des méthodes beaucoup plus concrètes, qu'on trouvera en appliquant la mécanique statistique à la biologie moléculaire.

A. LICHNEROWICZ: Je veux dire mon accord. Votre théorie fournit un "back-ground" fondamental pour la suite. L'image est excellente! . . . "Back-ground" dans lequel on mettra des choses assez variées.

I. PRIGOGINE: Au sujet de l'intervention de M. Lichnerowicz, je voudrais dire qu'il existe effectivement une certaine analogie formelle entre les problèmes que j'ai traités et des problèmes sociaux et économiques. Je pense même qu'il doit être possible d'aboutir à de tels éléments d'une théorie des structures sociales. Toutefois à un point de vue précis les problèmes dont j'ai parlé sont plus simples car je puis utiliser les conditions classiques de stabilité thermodynamique. Il faudrait voir si de telles conditions existent dans les problèmes sociaux. Il faut aussi, je crois, souligner combien les notions d'hétérogénéité et de complexité sont ambigues. Quant à moi je ne sais pas ce qui est plus complexe, une particule élémentaire ou un être vivant.

TH. VOGEL: Je voudrais toucher à deux questions. On a beaucoup parlé du caractère quantique des modèles qui ont été présentés. Je sais bien que "per fas et nefas perseverare diabolicum . . ." Cependant je n'ai pas été convaincu.

Il est bien évident que la théorie quantique doit couvrir, dans un certain domaine, tout ce que couvre la théorie classique, et doit en plus donner des renseignements complémentaires. Cela est vrai également de la théorie de la relativité, dont personne n'a parlé. Mais dans un domaine où la mécanique classique permet de rendre compte de tous les phénomènes qui ont été mentionnés, il est inutile de faire intervenir les quanta.

On nous a présenté, le cas d'illustration d'une lumière cohérente. Illustration qui pourrait être reprise, mot pour mot, des travaux de Bernouilli, sur la vibration d'une file de points matériels. Par conséquent, cela n'a rien de très nouveau. Il ne faut donc pas faire intervenir les quanta, tant qu'on n'a pas montré ce qu'ils peuvent donner, que la théorie classique ne peut pas donner.

Ma deuxième observation a trait à ce que disait M. Elsasser, et qui m'a vivement intéressé.

Il y a longtemps que je pense que l'outil le plus communément utilisé en physique – c'est-à-dire les équations différentielles – n'est pas un outil extrêmement approprié. Je pense, en tout cas, qu'en biologie mathématique, en biologie théorique, comme dans la plupart des théories que l'on peut être amené à bâtir, les équations différentielles, généralement utilisées en physique mathématique, ne sont pas l'outil le mieux adapté pour cette discipline. En tout cas, je suis convaincu – et M. Elsasser a achevé de me convaincre – qu'il n'est pas le plus adapté à la biologie théorique.

Alors, je voudrais signaler la possibilité et l'intérêt d'études sur les systèmes évolutifs sans unicité. Voici quelques années que je m'occupe des équations au paratingent qui peuvent couvrir une assez large part de ces problèmes, mais ces équations ne sont elles-mêmes qu'un cas particulier: il faut considérer des inégalités fonctionnelles qui permettraient d'avoir toutes les solutions possibles, l'ensemble des solutions possibles d'un système incomplètement déterminé.

La solution qui consiste à faire intervenir la probabilité est une fausse solution, à mon sens, parce que l'introduction de la probabilité suppose une axiomatique qu'on laisse généralement implicite et qui est beaucoup plus difficile à défendre que tout le reste de la théorie. Autrement dit, on fait une théorie qui est claire, facile, mais elle n'est valable que moyennant des hypothèses que généralement on ne spécifie pas et qu'il serait extrêmement difficile de vérifier par expérience.

L. TISZA: The discussions concerning the relation of physics and biology seem to be dominated by the intricacies of biology as if the nature of physics were clear to everyone. In reality, I believe, that a satisfactory characterization of physics is a difficult task, and one not to be ignored if the interdisciplinary discussion is performed with a reasonable measure of precision. The task is difficult because of the wide ramification of the branches of physics, and it is aggravated by the fact that all this is in a state of rapid evolution. I will have to confine myself to the discussion of a few characteristic points.

Let me consider the case of quantum mechanics that in the course of a few decades has undergone already essential changes. I am tempted to compare the course on quantum mechanics I took almost forty years ago in Göttingen with the course now being offered to second year undergraduates at M.I.T. The old course, among the first to be offered anywhere on the new discipline, was nominal that of Max Born, but actually it was given by his assistants, among them

Dr. Rosenfeld who is here with us today, and who may check up on my recollections. Well, the old course seemed paradoxical and outright mysterious, whereas the new one is being accepted with striking ease; in discussing the resolution of some of the "paradoxes" of quantum mechanics sometimes the hardest point is to convince the students that there is anything paradoxical involved at all. Needless to say, this comparison is not intended to cast any reflection on Professor Rosenfeld's teaching ability. It is, of course, to be expected that the novelty of a discipline wears off, the rough edges polished, and there are plenty of reasons why its teaching should become a great deal simpler. The point I wish to make is that the metamorphosis of quantum mechanics is more profound than might be expected on such grounds.

An elementary introduction to quantum mechanics necessarily starts with classical physics and a great deal depends on the kind of bridge that we construct between the two disciplines. The most striking difference between the above mentioned two stages of quantum mechanics is that they are tied in with very different parts of classical physics. In fact, I am convinced that the key to the clarification of most of the paradoxes of quantum mechanics is that we have to come to grips with some of the paradoxes and illusions of classical physics. The first illusion to be given up is that there *is* such a thing as a coherent body of classical physics. It is, indeed, well known that Newtonian physics had from the outset two main departments: first, an inductive phenomenological one in which the objects of everyday life and of the laboratory are taken for granted; and, second the analytical mechanics of rigid bodies and mass points. To the extent that this mechanics is applied only to macroscopic motion, these two departments are compatible with each other. This is no longer the case for the wider interpretation of Newtonian mechanics in which the validity of this discipline is postulated even for the smallest, atomic constituents of matter, and where it is assumed, or rather taken for granted that the entire phenomenological physics is reducible to mechanics. For the sake of brevity I shall refer to the two departments of classical physics as PCP (phenomenological classical physics) and MCP (mechanistic classical physics) respectively. The wide range of achievements of classical physics belong primarily to PCP, but its philosophy is altogether dominated by MCP. We know at present that PCP is not reducible to MCP. However, the origin of this failure is not as well understood as it might be. I wish to introduce a few concepts in the hope of shedding some light on the situation.

There are two types of regularities discernible in natural phenomena that are in a way complementary to each other. The first is the well known determinism of classical mechanics. I like to call it *temporal determinism* in order to emphasize that we are dealing with temporal sequences in which the arbitrarily chosen initial state determines the state at a later time. The initial state itself is arbitrary in the sense that it is not restricted by a law of nature within this discipline. This kind of ordering of natural phenomena was distilled from celestial mechanics.

The second type of order manifests itself most obviously in chemistry, say the periodical table of the elements, in which we find the systematization of certain configurations of nuclei and electrons forming the chemical elements. Such configurations are very much favored by stability among infinitely many other configurations that are not observable except in a most transient fashion. Some years ago I have suggested that this type of regularity be called *morphic*. I believe that the success of quantum mechanics is in a large measure due to the fact that this discipline provides a mathematical expression to morphic ideas. Thus, the quantum mechanical "pure state" can be conceived as the ultimate of chemical purification and the samples of a class of systems in the same pure quantum state are absolutely identical to each other. This property may be designated as "morphic invariance". It is also noteworthy that in quantum mechanics temporal and morphic considerations appear jointly in a consistent scheme. In strong contrast with this situation MCP has a purely temporal character, whereas PCP deals with the world as it is and implicitly contains morphic elements. Experimental spectroscopy is a good example for morphic aspects appearing in experiments set up entirely by classical means.

The granting to morphic invariance an independent conceptual status that cannot be reduced to temporal determinism enables us to envisage some of the problems raised from a fresh perspective.

The replacement of MCP by quantum mechanics no longer appears as the replacement of one mechanics with a somewhat different variant, but a fundamentally new conceptual element, namely the morphic point of view, is added to the theory. This explains why the traditional introduction of quantum mechanics as an analog of classical mechanics has a purely formal character giving no allowance to intuitive conceptual understanding. In contrast, the new quantum mechanics referred to above builds a bridge between quantum mechanics and PCP and the transition is a great deal smoother since both disciplines contain morphic elements.

I wish to comment now from the point of view just outlined on Dr. Elsasser's discussion of homogeneous classes. This concept has a clearly morphic character and I agree with Dr. Elsasser that it is of crucial importance for the discussion of the relation of biology and physics. However, I must take exception to the claim that physics deals *only* with homogeneous classes. First of all, we must not speak summarily of all of physics. Thus, MCP knows nothing of homogeneous classes. This concept emerged only within quantum mechanics as the set of systems in the same pure state. Second, quantum mechanics deals not exclusively with homogeneous classes, but contains actually rules for constructing more complicated situations. Let me mention only that we take the homogeneous classes of electrons, protons and neutrons and we build up the classes of nuclei, atoms and molecules. All of these systems can exist in homogeneous classes of pure quantum states, but in actual practice we are more likely to encounter them as various kinds of

mixtures of homogeneous classes, or more or less random selections from such.

There can be no doubt about it that biology deals *par excellence* with morphological properties and that morphic quantum mechanics has a great deal better chance to serve it as a fundamental theory than MCP ever had; it certainly goes a long way in providing a conceptual basis for molecular biology. Nevertheless, Dr. Elsasser may have a point in emphasizing that biological systems present us with a degree of complexity much beyond anything we have learned to cope with on the basis of the present day quantum mechanics geared to deal with physical systems. Yet would it not be foolhardy to claim that quantum mechanics has reached its final form? While no one can predict with confidence the evolution of quantum mechanics in the future, the prediction that is most likely to come to grief is one that would rigidly limit its adaptability and eventual scope!

L. ROSENFELD: This was a friendly challenge to me to express an opinion on the present state of quantum theory, compared to what it was forty years ago. Now, we have learned very much in all these years, of course, but in a sense we may also say that quantum theory, in its conceptual frame-work, is much the same to-day as it was then. What we have achieved, essentially, is a better delimitation of its domain of validity. All our physical theories operate with strongly idealized concepts, and the problem is to determine the limits within which such idealizations are useful tools for the analysis of the phenomena. Within these limits, we may well say that a theory that has stood the test of experience has acquired a perennial validity. So it is with the theories of classical physics, so it is with quantum mechanics.

We know that the biological processes, in their molecular aspects, fall within the limits of validity of quantum mechanics – often even within the range of application of the classical approximations to the quantal laws – and this makes quantum mechanics directly relevant to molecular biology, as has been emphasized by my colleagues this morning.

There is, however, another, more indirect way in which quantum theory may be of some help to biology: it concerns an epistemological problem which has been the object of long and confused debate in the course of history and is still widely regarded as a bone of contention among biologists. Will a physico-chemical analysis of the molecular processes underlying the biological phenomena provide a complete, exhaustive description of these phenomena, or must one expect that specific, non-physical concepts will be needed for this purpose? In this connexion, the concept that immediately comes to mind is that of "function", the usefulness of which in biological investigation nobody will deny. And the idea of function, with its implication of finality, seems to be incompatible with the type of causality exhibited by a purely physical description.

Now, in trying to account for quantal phenomena physicists have been led to recognize the existence of a logical relationship between concepts, to which the

name of complementarity has been given, which makes it possible to use without danger of contradiction concepts which are mutually exclusive, but nevertheless adequately describe certain aspects of experience. This possibility arises from the fact I stressed before, that concepts are idealizations of limited validity; contradictions only arise when they are stretched beyond such limits, and are avoided if the limits are properly recognized.

In this sense, there is certainly room in biology both for a full, unrestricted physico-chemical analysis of the molecular processes on the one hand, and a description of the functional aspects of the biological processes on the other. These two points of view should not be opposed to each other, but fruitful use could be made of them in a complementary fashion.

E. G. D. COHEN: I would like first to raise a general question. In many lectures and discussion remarks it has been tacitly assumed that the main connection of biology and theoretical physics should be through quantum mechanics. This may well be so but this morning already I raised the question on account of Dr. Fröhlich's lecture whether not in some cases analogies with *classical* statistical mechanics might be helpful for the understanding of some biological phenomena. On account of Dr. Cowan and Dr. Elsasser's lectures I would like to raise another question, namely one concerning the proper macroscopic description of a many particle system in physics. It seems to me that both Dr. Cowan's and Dr. Elsasser's lectures dealt with an analogous problem in biology. If in physics, the system is in thermal equilibrium the macroscopic variables to describe it are obvious. However, for a system not in thermal equilibrium the proper macroscopic description is in general far from obvious and usually unknown. The problem here is not only: what are the appropriate macroscopic variables for the system but also how are these variables related to the microscopic properties of the individual particles of which the system consists.

A second question relates more in particular to Dr. Elsasser's lecture. Could he perhaps say again in how far a biological system differs *essentially* from a many particle system in physics. His wording of the properties of a biological system could – as far as I can see – be taken directly from a textbook of statistical mechanics.

W. M. ELSASSER: Je ne crois pas que la différence entre la mécanique quantique et la mécanique classique soit considérable à cet égard. Il y a toujours deux niveaux dans l'exemple standard, nous avons le niveau microscopique. Ensuite, le niveau macroscopique, la pression, la température, etc. . . .

Je ne sais s'il y a ici des biologistes empiriques (ils sont d'habitude rares dans les réunions comme celles-ci): ils conviendront avec moi et vous diront qu'un organisme a une structure extrêmement compliquée à tous les niveaux: au niveau des angströms, au niveau des microns, au niveau des millimètres, etc. Là, il y a

une structure dans une structure – dans une structure – dans une structure – : comme on l'a déjà dit, c'est la caractéristique essentielle d'un organisme. Donc, vous ne pouvez pas appliquer la mécanique statistique: le processus d'organisation est trop compliqué pour le faire. Naturellement on tentera cette application puisqu'il n'y a pas d'autre outil. Mais il faut y être extrêmement prudent.

Ma deuxième observation est un peu plus subtile: dans le passé il y avait une distinction très claire entre ces deux grandes catégories: le déterminisme et les statistiques. S'il y a des mathématiciens ici, j'espère qu'ils ne se vexeront pas du terme "statistiques" au lieu de "calcul des probabilités". Il y avait donc déterminisme et statistiques. L'hétérogénéité qui apparait ici est une catégorie essentiellement différente de la statistique. Car, en statistique, vous supposez, selon l'axiomatisation acceptée par les mathématiciens, que vous pouvez former n'importe quelle moyenne, quelle qu'elle soit. L'essence d'un système hétérogène est que vous ne pouvez point prendre toutes les moyennes. Vous pouvez en prendre certaines. Si je pouvais prendre toutes les moyennes, je serais reduit immédiatement à la biologie mécanistique. Quant à la mécanique quantique, je dirai, par exemple: j'ai une matrice statistique et je peux définir tous les opérateurs que je veux, et je peux déterminer, mathématiquement, la moyenne de ces opérateurs dans l'ensemble des échantillons. L'hypothèse admise est qu'on peut toujours le faire. Von Neumann a toujours fait cela, comme mathématiques. L'axiomatique de Von Neumann est fausse, à mon avis du point de vue physique: vous n'avez pas assez de spécimens, pas assez d'homogénéité pour pouvoir produire ces moyennes par des procédés opérationnels. Je sais que c'est extrêmement difficile à saisir. Mais c'est la différence essentielle entre l'hétérogénéité et les statistiques. A moins que vous n'ayez cette différence et que vous ne l'ayez saisi, on ne peut pas comprendre ce qui importe en matière de biologie. Mon temps n'était pas assez long pour développer cette pensée en détail.

H. C. LONGUET-HIGGINS: I want to make one or two disconnected remarks first, and then to say something more connected. First of all, a comment on Dr. Elsasser's contribution. It seems to me to be too simple to say that physics deals with homogeneous classes. Solid state physicists deal with such things as imperfect crystals, and no two imperfect crystals are alike.

My second point concerns a comment made by Dr. Rosenfeld on Dr. Fröhlich's contribution which we have been discussing with much interest. Dr. Fröhlich seems to have contributed a suggestion about a possible new phenomenon to look for. It seems to me that the problem we really have in front of us is not to find new phenomena but to find concepts for the interpretation of existing phenomena. Plenty of strange things happen in Biology, without introducing any more. I would suggest that what we really need to do is to find some way of coping with the phenomena we do know about. Can I just make a very short list

of a very few things which seem to me to be outstanding characteristics of biological systems that are not found in the inanimate world.

(1) Evolution,
(2) The processing of information by organisms – for example in the central nervous system of vertebrates,
(3) Morphogenesis.

I think we would not feel the need of new fundamental concepts for discussing the theory of evolution; there are already very good existing concepts such as variation, mutation, selection and so forth which have proved themselves in this connection. But I would like to make one or two suggestions about the other two phenomena.

First of all, the question of information processing by the individual organism. In what way should we look at the relation between the stimuli and the responses? Here it seems to me that one could use the sort of ideas that Dr. Cowan has been describing to us. These come from control engineering, where one talks not so much about the physical nature of the processes but their mathematical description.

Now a word about morphogenesis. We are all of course amazed by what happens when we sow a seed in the garden and up comes a rose. It is a most fantastic phenomenon. Now what kind of ideas do we need in order to understand this? May I suggest that the kind of idea one wants is that of a computer program and its output. Perhaps this sounds rather low-brow, but the mathematicians are now busy developing the theory of computer programs and the theory is concerned with the classification of different types of program and their different modes of implementation. There is a quite remarkable formal resemblance between feeding a paper tape into a certain environment and getting out a complicated data structure, such as a set of mathematical tables, and on the other hand pushing into a cell a long double molecule with bases all along it and getting out a complicated physical structure which is an organism.

My feeling is, therefore, that the sort of concepts which we need for understanding morphogenesis – which is an outstandingly biological kind of thing – are perhaps the same sort of concepts that one needs for understanding the scope and the limitations of computer programs. And it seems that there is some hope of making progress in this direction, because, after all, computer programs are a human invention and people who work with computers may be expected to have a pretty clear idea of what they are up to. In fact, the problems are really not physical problems at all, but mathematical and logical ones.

J. POLONSKY: Ma première remarque concerne la "querelle" entre l'entropie thermodynamique et l'entropie de l'information. Cette "querelle", évoquée par M. Lichnérowicz, me fait penser à une petite histoire que je vais vous confier:

Une question centrale posée par la cybernétique quantique pourrait être formulée comme suit:

Quelle est l'origine physique des contraintes collectives qui apparaissent dans un système polyatomique? ou, en d'autres termes:

Les contraintes collectives dans un système étant équivalentes à une certaine entropie négative, la question se pose: Qui paie le prix de l'entropie négative qui apparait dans le système global?

Je vais essayer de résumer ici quelques éléments de réponse qui découlent de l'étude préliminaire sur un plan qualitatif (l'étude quantitative est en cours):

1. L'ordre, ou toute forme d'organisation dans un sytème polyatomique, *provient d'une délocalisation des contraintes des probabilités* dans les composants atomiques moléculaires ou supramoléculaires, par voie de couplage. On peut parler d'un véritable transfert d'ordre ou d'invariance de structure de l'échelle des composants vers l'échelle du système.

2. Grâce au couplage, la structure collective devient moins aléatoire, en revanche, la structuré individuelle de chaque composant devient plus aléatoire. Les contraintes électroniques hautement quantifiées dans chaque atome pris isolément, diminuent dans la structure polyatomique au bénéfice des corrélations créées entre les divers états électroniques et au bénéfice des contraintes vibrationnelles et rotationnelles.

3. La délocalisation des contraintes au cours du couplage découle directement de la délocalisation des cellules quantiques prises dans l'extension en phase à 6 dimensions, cellules occupées par les électrons les plus mobiles appartenant aux structures atomiques ou moléculaires. Les nombreuses corrélations qui apparaissent dans le volume commun à 6 dimensions (3 de position, 3 de moment) et l'énergie d'échange qui s'y rattache, sont à l'origine d'effets coopératifs spatio-temporels et forment ensemble la base de l'organisation structurale et fonctionnelle du système.

On pourrait évidemment se poser la question suivante: Quel intérêt pratique peut présenter une telle approche pour le biologiste?

Je vais tenter de répondre brièvement à cette question.

L'organisation en biologie est souvent représentée par une pyramide d'organisations faiblement couplées entre elles. Le transfert d'ordre au cours d'associations successives devrait, de ce fait, y être beaucoup plus modéré que dans les structures inorganiques. On peut ainsi procéder pas à pas au cours de l'étude de la complexification des structures biologiques, en partant de molécules vers des macromolécules, des macromolécules vers des assemblées de macromolécules, etc. et évaluer à chaque étape sous quelle forme apparait l'ordre collectif toujours égal ou inférieur à la perte de l'ordre inviduel dans les composants (sans tenir compte

de l'entropie négative complémentaire apportée éventuellement par une source d'énergie externe).

A titre d'illustration, examinons quelques modèles simples. Précisons tout d'abord la nature physique des contraintes ou d'invariants dans une structure à électrons très localisés (atomes ou petites molécules). Il est connu que les cellules occupées par des électrons localisés sont caractérisées par un très petit volume de position ($\Delta x \cdot \Delta y \cdot \Delta z$) et par un très grand volume de moment ($\Delta p_x \cdot \Delta p_y \cdot \Delta p_z$). Dans le cas d'une telle structure, on peut dire que les contraintes des probabilités, ou l'information structurale, sont essentiellement de nature spatiale et sont très faiblement impulsionnelles. Inversement, si l'on examine une structure riche en électrons très délocalisés (par exemple des cristaux), les cellules de phase occupées par des électrons délocalisés sont caractérisées par de très petits volumes de moment et par de très grands volumes de position. Il en résulte que les contraintes d'information dans une structure à électrons fortement délocalisées sont essentiellement de nature impulsionnelle et se trouvent caractérisés par la structure de bandes. Dans le cas de systèmes biologiques, on a souvent affaire à des structures conjuguées où la délocalisation des électrons mobiles π (et des cellules correspondantes) est différenciée et s'étend entre les deux limites examinées tout à l'heure. Dans de telles structures, les contraintes d'information sont mixtes: elles sont spatio-impulsionnelles. Plus la délocalisation d'une cellule augmente, plus sa structure et son information tendent à être impulsionnelles. Par contre, son information spatiale perd en importance et vice-versa. Aux limites, on peut dire qu'en chimie l'information est spatiale tandis qu'en électronique macroscopique, l'information est impulsionnelle et la seule variable significative devient le temps. En biologie, il faut tenir compte de l'espace et des impulsions conjointement.

L'approche par la méthode du transfert d'ordre permet d'obtenir d'autres résultats qualitatifs intéressants. En particulier, on sait qu'une cellule très localisée est protégée par des barrières quantiques élevées. Dans un atome, par exemple, l'intervalle entre l'état fondamental et le premier état excité d'un électron périphérique varie de 5 à 15 eV. Pour obtenir un bit d'information sur la structure atomique, il faut payer un prix énergétique élevé. Par contre, dans le cas du cristal, les cellules délocalisées sont protégées par des barrières quantiques très faibles de 10^{-20} eV environ. En l'absence de fluctuations thermiques, le prix du bit d'information dans un tel cas aurait été très bas. Néanmoins, à la température normale, il est nécessaire de tenir compte des fluctuations et toute cellule à caractère informationnel doit être protégée par une barrière supérieure à kT ($kT = 0.025$ eV pour $T = 300°K$). De cet examen qualitatif, on peut tirer quelques conclusions intéressantes sur le plan de la cybernétique biologique.

1. A la température normale, des structures optimisées (capables de fournir des informations structurales suffisamment sûres avec le minimum de dépense d'énergie) devraient être constituées par des cellules de phase protégées par des

barrières quantiques de 4 à 10 kT, c'est-à-dire de 0.1 à 0.25 eV environ, selon la probabilité d'erreur admissible.

D'autre part, les quanta d'énergie de la source biologique devraient être légèrement supérieurs à 0.25 eV, compte tenu du rendement de conversion énergie/information.

2. Les conditions ci-dessus sont parfaitement réalisées dans le cas des systèmes biologiques.

En effet, dans les structures biochimiques, le bit d'information est souvent déterminé par la rupture d'un pont hydrogène (énergie de 0.1 à 0.25 eV) et la source universelle d'énergie, l'ATP, fournit des quanta de 0.4 eV environ.

Comme autre exemple d'application de cette méthode d'approche, examinons le modèle cybernétique de l'ADN. On peut distinguer, dans l'ADN, deux structures électroniques collectives: celle du *squelette* comportant tous les électrons localisés de la double hélice et des plateaux basiques et celle des *domaines informationnels* constituée par des pools d'électrons π. L'invariance du squelette est essentiellement de nature spatiale et provient d'une perte partielle d'invariance spatiale dans chaque atome faisant partie du squelette. Le gain en contraintes collectives dans le système est l'équivalent d'une très basse température statistique de l'ADN.

D'autre part, l'invariance de la structure collective des électrons π est de nature spatio-impulsionnelle, et les nombreuses corrélations entre les cellules de phase des électrons π sont à l'origine de la grande spécificité informationnelle de chaque plateau basique. Le couplage, enfin, entre les électrons π des plateaux basiques voisins fournit une nouvelle invariance collective de nature informationnelle d'où peut dériver un mode multiplex dynamique très spécifique de l'ensemble vis-à-vis des molécules environnantes.

Nota: Aux effects coopératifs d'états électroniques il faut ici, bien entendu, ajouter les effets coopératifs des vibrations et rotations moléculaires.

En résumé:

1. Dans les molécules, le transfert d'invariance crée une spécificité chimique essentiellement spatiale tridimensionnelle qui confère à ces molécules une *fonction de nature informationnelle*. Dans les cristaux, le transfert crée une spécificité électronique essentiellement impulsionnelle caractérisée par la structure des bandes. Cette structure ordonnée confère aux cristaux leurs excellentes propriétés de *convertisseurs d'énergie* à l'échelle macroscopique. Dans les molécules et agrégats des molécules, le transfert développe une invariance mixte spatio-impulsionnelle où un squelette tridimensionnel abrite contre des fluctuations, une riche information hexadimensionnelle spécifique. Une telle structure collective forme une organisation et peut exercer sur son environnement moléculaire, des effets puissants

d'asservissement ou de catalyse, c'est-à-dire modifier profondément les probabilités des réactions chimiques et des conversions d'énergie à l'échelle microscopique.

2. Au fur et à mesure de l'association des structures différenciées, les effets coopératifs des cellules de phase créent des nouvelles propriétés physiques (voire biologiques, physiologiques, etc.); celles-ci ne sont que des *effets intégratifs qui dérivent de l'ordre quantique transféré des composants vers le système collectif.*

Dans un système où l'ordre et l'information potentielle atteignent un degré tel que le système est capable d'asservir une énergie d'origine externe (capacité de transformer une énergie au bénéfice de sa propre organisation, comme la photosynthèse et la phosphorylation oxydative en biologie) nous nous trouvons en présence d'un système cybernétique naturel. Ce pas est décisif car il offre à une structure organisée des perspectives immenses d'asservir l'environnement, soit en se multipliant au détriment du milieu, soit en organisant ce milieu à son profit. Les limites de l'asservissement se trouvent essentiellement déterminées par les ressources du milieu et par la compétition avec des systèmes analogues. La "finalité" biologique et la sélection naturelle dérivent ainsi directement de la capacité d'asservissement des systèmes biologiques.

P. O. LÖWDIN: I would like to make a short comment on the lectures given by Dr. Fröhlich and Dr. Prigogine. In the discussion, there seems perhaps to be some contradiction between the points of view expressed in these two lectures. In my opinion, there is no contradiction, since in reality the two topics discussed refer to different parts of the theory of the treatment of biological systems.

In order to explain what I mean, I would like to refer to fig. 1, where I have drawn an axis representing the degree of "order" of a system. On the extreme left of this axis, one has a point describing a system in "complete order", for instance a crystal at absolute zero of temperature. On the other end of the axis, one may have a system characterized by complete "disorder" or random-phase distribution. It is well known that all the important concepts of thermodynamics are associated with systems characterized by a certain disorder, and some of the properties of these systems are described by the concepts of entropy, free energy, etc. Phenomena occurring in such a disordered system are often described as "incoherent". Dr. Prigogine has discussed some of the fundamental properties of such disordered

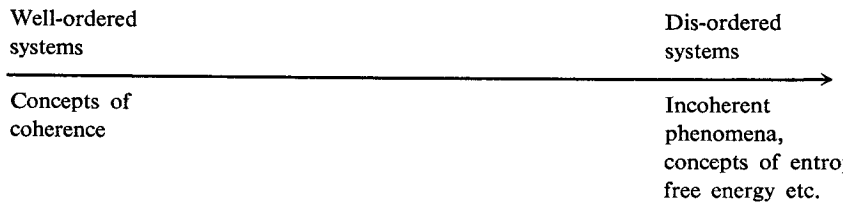


Fig. 1. Comparison between ordered and disordered systems in nature.

systems, whereas Dr. Fröhlich has in his talk described phenomena which may best be characterized as coherent or wellordered with respect to phases etc.

In quantum mechanics, the properties of random-phase systems were first discussed by Pauli and Dirac, and Oskar Klein showed that one could derive an irreversible law in quantum mechanics from the randomphase postulate. In biology, the degree of order may vary from one type of system to another. Certain types of substances, like blood, are to a large extent random mixtures and may necessarily be described as liquids, whereas certain cells are so well-ordered, that they are often described as "fluid crystals". Different types of theories are hence needed for treating different types of biological systems.

In treating biological bodies, one should certainly study the macroscopic behaviour by means of classical mechanics and, in the next approximation, one may need thermodynamics and classical statistical mechanics, to understand the general behaviour of the transport phenomena and similar processes inside the body. However, when going inside the cell, it is necessary to go into molecular and submolecular biology, and one is then going to look at rather well-ordered systems of fundamental particles which are subject to the laws of modern quantum theory.

In theoretical biology, the use of statistical mechanics is rather well established, whereas the importance of coherent phenomena is not so well understood. In his example, Dr. Fröhlich has chosen a rather "macroscopic" coherent phenomenon in analogy to superconductivity and superfluidity, and I would here like to mention another example of an even simpler character–the covalent chemical bond.

The coherent nature of the ordinary chemical bond, of fundamental importance in chemistry and biochemistry, becomes particularly clear in the molecular-orbital picture. Let us consider a diatomic molecule, where the valence electrons may occupy the atomic orbitals a and b. By linear combination, one may here construct either a "bonding" molecular orbital of the type $\varphi = a + b$ or an "anti-bonding" molecular orbital of the type $\chi = a - b$; see fig. 2. From the hydrogen

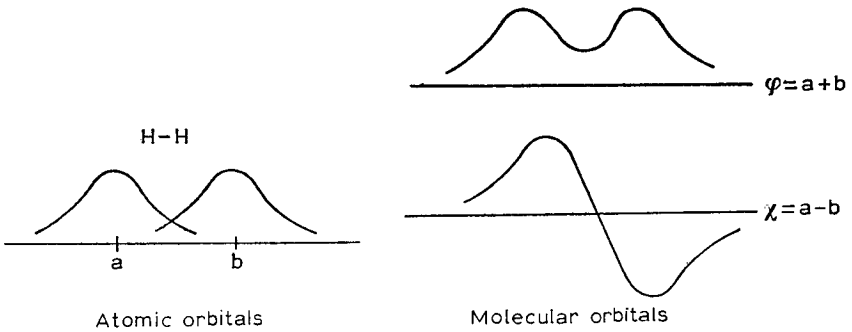


Fig. 2. Comparison between the bonding orbital $\varphi = a + b$ and the antibonding orbital $\chi = a - b$ in the molecular orbital model of the hydrogen molecule; note that the phase factor ± 1 in front of b leads to an energy difference of about 8eV.

molecule, one knows that the orbital energies may differ by as much as 8eV, which is an enormous quantity in comparison to the thermal energy fluctuations given by kT, and which depends essentially on a phase factor – the coefficient ± 1 in front of b.

The quantum-mechanical coherence can hence give a certain definite order and chemical structure to a biological system, in spite of thermal fluctuations and statistical irregularities. This point was strongly emphasized by Schrödinger in his famous lecture series in 1943 about "What is Life?". He said that many biological processes are so precise that it seems as if they would occur at absolute zero temperature ($T=0°K$), in spite of the fact that they occur at $T=310°K$. This can only depend on the fact that, even at the latter temperature, the thermal energy kT is very small in comparison to the quantum-mechanical energy differences.

From this point of view, quantum mechanics becomes of importance in biology when one starts studying the innermost structure of the cells in terms of elementary particles – electrons, protons, neutrons, photons, etc. – and in terms of atoms and molecules, linked together by covalent bonds, ionic bonds, and hydrogen bonds. One difficulty is connected with the fact that most of our familiar macroscopic concepts – entropy, free energy etc. – are well-defined for disordered systems, whereas the corresponding conceptual framework for ordered systems is still partly missing.

I believe that these questions will be of even greater importance in the future, and one may wonder what contributions quantum mechanics may have to offer to the development. It should be remembered that quantum mechanics is basically only a theoretical tool for handling experimental information. It is based on the Schrödinger equation:

$$\mathscr{H}\Psi = -\frac{h}{2\pi i}\frac{\partial \Psi}{\partial t},$$

and the problem is to determine the solution Ψ corresponding to the "initial condition" $\Psi=\Psi_0$ for $t=t_0$. The solution may be written in the form

$$\Psi(t) = U(t; t_0)\,\Psi_0,$$

where $U=U(t; t_0)$ is the evolution operator connected with the system. Today one knows many methods to determine the evolution operator mathematically, and the big question is instead: "How does one determine the initial wave function Ψ_0 to absolute value and phase for a given physical situation at $t=t_0$"?

The stationary states of a system are determined by the eigenvalue problem

$$\mathscr{H}\Psi = E\Psi,$$

underlying the theory of atomic and molecular spectra, and, even if this specia. problem is of a more ab-initio-character, one should remember that most problems

in molecular biology are of time-dependent nature and require initial conditions obtainable only from the experimental experience.

In this connection, one should also remember that quantum mechanics is a special case of quantum statistics, which is based on the use of density matrices Γ satisfying the time-development equation

$$\Gamma(t) = U\Gamma_0 U^{\dagger},$$

where Γ_0 is the density matrix for the "initial state" at $t = t_0$. This little analysis implies that, even if quantum mechanics can provide a certain conceptual framework for the discussion of the behaviour of elementary particles in molecular and submolecular biology, all the initial conditions have to come from experiments.

J. D. COWAN: I would like to comment on Dr. Cohen's and Dr. Longuet-Higgin's remarks concerning the microscopic and macroscopic aspects of biological modelling.

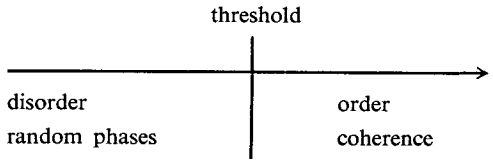
There are three cases where statistical mechanics has been applied to biological problems without any connection whatsoever with quantum mechanics. One is the generalization of Volterra's population mechanics carried out by E. H. Kerner. Here it is very natural to use classical statistical mechanics to describe the interaction between predatory species and their prey. It turns out that it is very useful to use statistical mechanics, because if one examines ecological data, for example, the incidence of foxes caught in Labrador over a long interval, unless one knows what to measure, what parameters of the ensemble to choose, it is very difficult to determine what is going on. Corbet, Fisher and Williams worked on population mechanics without really understanding the nature of the underlying ensemble, and very cleverly produced empirical distributions for the catches that fitted the data. It was only when Kerner introduced the Gibb's ensemble and showed that the concept of temperature was so useful that he was able to deduce the CFW theory and to infer just exactly what was going on in the population as a whole.

Recently I have done something very similar for neuron populations. Microelectrode recordings are currently being made of individual neuronal activity without sufficient knowledge of the relevant population activity. Here, again, one needs to know something about the ensemble before one can study interactions. B. C. Goodwin has recently worked out a Gibbsian statistical mechanics for Protein synthesizing systems, using the Jacob–Monod circuits. He has shown that there are oscillations in Protein concentrations that result from the feedback inhibition of the production of Messenger RNA by the by-products of metabolism. Again, there is a useful ensemble here, but it starts to become a little too difficult, because the interaction between units, i.e., between protein synthesizing circuits, starts to become a lot "stronger" than in the other cases.

But all this is in the equilibrium case. It is in the non-stationary case that things really become difficult, and I think it is here that the basic biological

problems arise, and here that the concept of "information" enters. I use the term "information" not in the static sense of the communication engineer, but as originally introduced by Wiener. He defined information as the name for the process by which the organism adapts to its environment and makes the results of its adaptation effect the environment. Information, then, is a relation between organism and environment. But this means that associated with information processing, there must be a change of state of an organism. It must "switch" from one state to another. However, apart from the necessary minimum requirement of about one "kT" per "bit" to signal the switching, there is no other fundamental connection between information and energy, and I, therefore, view the equivalence of information with "Negentropy" postulated by Brillouin with reservation. The main issue is that of the stability of the states between which switching is to occur, and I was therefore very interested in Prigogine's remarks, in which he showed how both dissipative and non-dissipative phenomena are important for the stability of states of interacting substances. It is this kind of approach that will lead us to an understanding of the relation of microscopic to macroscopic biological phenomena, rather than any extension of quantum mechanics.

H. HAKEN: Dr. Fröhlich has stressed the importance of the concept of order in physics, particularly in superfluidity and also in lasers. We have further seen a diagram of order and disorder, which Dr. Löwdin suggests also for the formation of biological systems. On the left-hand side ("disorder") we have for instance the concept of entropy and random phases.



On the other side ("order") we have in this group the phenomenon of coherence. We had another discussion as to where quantum mechanics comes in and where classical physics begins. I want to present a model which we have treated exactly and which shows the complete transition from disorder to order. It means one can show how a completely random system organizes to become a completely organized (or coherent) system. If one makes such specific statements one has to have a very simple model which is fortunately provided in physics by the laser.

First I have to make a few comments how lasers work. I am apologetic to the experts and to the other participants because one can read it in every newspaper how lasers work. But nevertheless we have to make a few comments in order to show the essential points. A laser consists of two mirrors with an active material in between. The role of the active material is to emit light. If you excite the atoms

they start to emit light in all directions. Thus the energy is distributed over an enormous number of degrees of freedom of the light-field.

In order to make the laser work we have to reduce the number of degrees of freedom. This is one of the points Dr. Fröhlich has made. If you have these two mirrors you can select those waves which go in the axial direction. If such a wave hits the mirror it is reflected back and forth. So this mode of excitation has a chance to stay a rather long time in the laser. This is the first means to reduce the number of degrees of freedom, because all other modes are now unimportant. In radio technique you would say you have a filter. The question to the biologist would be what is the analogue of a filter. We don't know.

Next we look only at light which is emitted in the axial direction and we consider the emission process in more detail. We have atoms which are excited at random and we know they emit light spontaneously. That means one atom emits a light wave at a certain moment while another atom emits another light wave, etc. So you have a random superposition of waves which corresponds to complete disorder.

Now let me turn to a mathematical description which shows quite clearly how the transition from disorder to order comes in. As you know we can describe a light field by electromagnetic waves with an electric vector E and we can decompose the electric vector in an amplitude which is time dependent $b(t)e^{-i\omega t}$ (ω: mode frequency) and a factor $g(x)$ which describes the spatial behaviour of the wave:

$$E = (b(t)e^{-i\omega t} + b^*(t)e^{i\omega t}) \cdot g(x).$$

I want to describe what happens to the amplitude $b(t)$ and how one may treat it in a quantum mechanical manner.

In quantum theory the light amplitude $b(t)$ is the creation operator of a light quantum. Then we can write the following equation for b or b^*

$$\frac{d}{dt} b^* = -\varkappa b^* + F(t) + \text{const. } b^* \sigma. \tag{1}$$

Because the light may escape a little bit through the mirrors its amplitude decreases. This is described by $-\varkappa b(t)$ in eq. (1). Then we have the process of spontaneous emission, which we have taken care of by a fluctuating force $F(t)$ acting on $b^*(t)$. F is a sum over the contributions of all atoms μ which emit light at random times with a certain "force" $F\mu$. I don't want to show how these forces describe spontaneous emission. I just mention that they are of both quantum mechanical and statistical nature.

The third term on the right hand side of eq. (1) represents the role of stimulated emission. An atom with two levels which is hit by a light wave absorbs light if it is in its ground state. We know that if the atom is in its upper state it performs the process of stimulated emission, i.e. the light amplitude is amplified.

According to eq. (1) the temporal change of $b(t)$ is proportional to the light

amplitude and to the degree of inversion. $\sigma = N_2 - N_1$ when we have N_2 atoms in the upper state and N_1 in the lower state.

We have an absorption if N_1 is bigger than N_2 and vice versa, i.e. the sign of σ is essential. If σ is positive the light wave increases, if σ is negative it decreases. Now we come to the second aspect of our problem which might be discussed to a large extent namely the concept of feedback, or with other words of self-control. We know that one can write a second equation for σ

$$\frac{d}{dt}\sigma = -\text{ const}' \cdot b^* b + \frac{\sigma_0 - \sigma}{T}. \tag{2}$$

The time derivative of σ decreases proportionally to the intensity of the light field. When thus the light intensity becomes too large σ decreases. This is compensated by the external pumping. The last term in eq. (2) describes this pumping, i.e. σ approaches a certain value σ_0 if there is no field b. But now as you may see we may integrate this equation in a simple way if the relaxation time T is short so that σ can follow adiabatically the light field:

$$\sigma = \sigma_0 - T \text{ const}' \, b^* b. \tag{3}$$

When we insert (3) into (1) we obtain a non-linear quantum mechanical equation

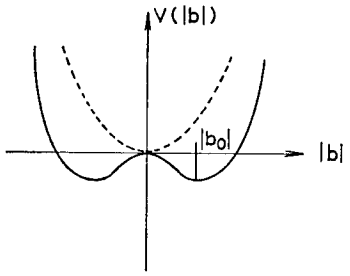
$$\frac{db^*}{dt} = -\varkappa b^* + F(t) + \text{const} \cdot b^*(\sigma_0 - T \text{ const}' \cdot b^* b), \tag{4}$$

which had been discussed in the *classical* domain by a number of physicists. What I want to show is that this equation with the noisy driving force $F(t)$ allows us to explain completely the transition of disorder to order.

a) *Disorder*: The force $F(t)$ is the sum of many contributions. When the light amplitude is very small we may neglect the non-linear terms. Then we have just a differential equation with a term which consists of many statistically independent contributions. As a consequence also b is a superposition of random contributions. Thus we find complete disorder, which is usually observed. Thermal fluctuation or spontaneous emission produce complete disorder.

b) *Order*: We now change the parameters σ_0 which describes the degree of inversion. We then come to a state which is stable. In order to explain this let me rewrite eq. (4) a little bit differently and let me add a term $\varepsilon \ddot{b}$, where ε is a small quantity

$$\varepsilon \frac{d^2}{dt^2} + \frac{db^*}{dt} + \varkappa b^* - \text{const} \cdot b^*(\sigma_0 - T \text{ const}' \cdot b^* b) = F(t). \tag{5}$$



This is now the equation of a particle moving in the potential field

$$V = -\text{const}'' \cdot \tfrac{1}{2}|b|^2 + \text{const}''' \cdot \{\tfrac{1}{4}|b|^4\}; \; \text{const}'' = \sigma_0 \cdot \text{const} - \varkappa$$

and subject to an additional force $F(t)$.

If σ_0 is small the potential looks like the dotted line. That means when we excite the "particle" (the light field) it falls down again so that it performs a damped oscillation.

On the other hand if the parameter σ_0 becomes bigger and bigger we find the potential given by a solid line. That would mean that the "particle" (or the light field) is now stabilized at a certain point b_0. This is a case of more complete order. One can show exactly that a classical quantity b_0 arises out of the quantum mechanical quantity $b^*(t)$ so that the light field is a classical number. You see if we have thermal or spontaneous emission fluctuations the light field relaxes to a stable c-number amplitude. Thus we have only small quantum fluctuations around a stable macroscopic state. If we increase σ_0 the hills of the potential around b_0 become steeper and steeper and so the effective noise which is produced by this spontaneous emission becomes smaller and smaller.

I shall not speak more about these things. Perhaps I should conclude with the following remark. When one looks at the statistics in the region a) where we had many independent contributions, then one finds a Gaussian distribution of $b(t)$ which corresponds to Bose-Einstein statistics. On the other hand if the non-linearity becomes important you may neglect the fluctuations and then you get a Poisson distribution. That means if one measures the light coming out of a laser while one changes the pumping parameter one may find a transition from complete disorder to order. This prediction was indeed experimentally checked in the meantime and fully substantiated. I think we have a very simple but also realistic model of such a transition.

H. FRÖHLICH: I should like to make a very little remark. This is very instructive of course, mathematically a very simplified model and it tells you how such an ordered oscillation can build up order and disorder. I think a corresponding model could be made in connection with the longitudinal mode of which I have spoken of. Of course these models with reflecting mirror would be biological molecular processes which are stimulated by the radiations. There is no emission of radiation. Instead there would be frictionnal terms. I think such a model could be developed.

L. ROSENFELD: I think that it is misleading to describe this as a classical effect because the quantity b_0 contains the parameter d, which is a quantal parameter, depending essentially on Planck's constant.

M. DALCQ: Ce n'est pas sans appréhension qu'un biologiste préoccupé des problèmes du développement et de la vie cellulaire se risque à intervenir après les

communications réellement transcendantes qui viennent d'être entendues, et qu'il n'a guère pu – il n'est probablement pas seul dans ce cas – saisir intégralement. Qu'il lui soit d'abord permis de remercier nos collègues spécialisés en physique théorique de l'effort qu'ils ont consenti pour permettre aux biologistes d'approcher la démarche de leur pensée.

J'imagine, à tort ou à raison, qu'il peut être utile de confronter avec leurs points de vue celui qui se dégage d'une fréquentation assidue de la vie cellulaire, notamment sous les aspects spécialement constructifs qu'elle prend dans le développement.

Accordons-nous d'abord sur cette notion très générale que l'être vivant, quel que soit le règne dont il relève, est, sauf si ses dimensions sont très réduites, d'une grande complexité, qu'il est caractérisé par une organisation comportant des niveaux emboités les uns dans les autres, que ses activités fondamentales sont extraordinairement diverses et variées. Permettez-moi maintenant d'envisager spécialement cette activité biologiquement universelle qu'est la division cellulaire. Cette activité si générale semblerait, à première vue, devoir être pratiquement univorme—Or, ce n'est pas le cas.

Ses prémisses, qu'il serait trop long de résumer, comportent déjà bien des variantes, tant au point de vue cytologique que biochimique, et ce qu'on en sait reste d'interprétation difficile. Elles aboutissent en général, à l'exception de types cellulaires inférieurs, à l'édification d'un appareil mitotique dont la forme, le plus souvent en fuseau, et la structure varient considérablement. Lorsqu'alors la division se réalise, on s'attendrait à observer uniformément un allongement du corps cellulaire dans le sens de l'axe du fuseau, puis un étranglement médian perpendiculairement à cet axe. Or, dans nombre de cas, il n'y a pas de déformation préalable, et c'est par un remaniement interne qu'une cloisonnement s'accomplit. On voit donc que la cellule recourt à des mécanismes divers pour assurer un même résultat.

Je voudrais maintenant faire une remarque de portée plus générale, à savoir que, dans l'existence de tout être vivant doué d'une organisation quelque peu complexe, il convient de distinguer deux phases, celle de devenir ou d'ontogenèse, celle d'état définitif, souvent dit adulte.

Dans ce dernier, l'organisation spécifique est acquise, il s'agit d'un système morphologiquement stabilisé, bien que tous ses matériaux constitutifs soient constamment renouvelés. Il n'en va pas seulement ainsi pour les populations de molécules disposées au sein des cellules, mais aussi à la surface de celles-ci, dans leur membrane limitante, dont la structure est si importante. Dans cette phase d'apparence statique, on peut, dans certains cas, comme M. Duchesne l'a déjà rappelé, suspendre momentanément le cours des processus vitaux soit par dessication, soit par refroidissement par un procédé adéquat. Il semble bien que la possibilité si remarquable de cet arrêt réversible soit liée à celle de respecter intégralement la microstructure, tout en suspendant les échanges. C'est dire que la notion de vie est, pour la période d'état, moins liée au métabolisme qu'à la forme.

C'est ce qu'affirmait implicitement ce matin M. Fröhlich, c'est ce dont Albert Brachet avait une vision très claire lorsque, il y a juste quarante ans, il intitulait un de ses ouvrages généraux: "la Vie créatrice des formes".

Cette allusion m'amène à considérer la période ontogénétique. Pour celle-ci, Courrier et Marois ont montré que l'hypothermie suspend l'ontogenése chez le rat, ce qui n'étonne pas, car on connaît, dans la nature, certains exemples de période stationnaire dans le développement. En tous cas, la phase créatrice se caractérise par une évolution intense du métabolisme. Il ne s'agit guère de cycles, de processus se répétant périodiquement, comme c'est le cas dans l'organisme adulte, mais de progression, notamment quant à la synthèse rapide de macromolécules, particulièrement de protéines, ce qui implique un perfectionnement marqué de l'équipement enzymatique. Cependant, aux yeux des embryologistes, la complication progressive du chimisme, avec son perfectionnement graduel, n'est qu'un ordre de faits, sous-jacent à la morphogenèse en soi. Celle-ci suppose l'acquisition de structures localisées à certaines régions du germe et qui préparent l'apparition des organes primordiaux. Il est indispensable de rappeler ici le cas des Amphibiens, chez lesquels les premiers indices de structure morphogénétique surgissent par différenciation du *cortex* de l'oeuf fécondé. Ce qu'on nomme ainsi est plus que le plasmolemme; c'est à la fois celui-ci et une fine pellicule de cytoplasme périphérique. Avant la fécondation, on peut dire, en schématisant quelque peu, que sa structure est uniforme. A un moment précoce du développement, des particularités apparaissent dans une certaine région corticale en forme de croissant. Cette différenciation va régir la polarité céphalocaudale et la symétrie bilatérale du nouvel organisme. Je n'en dirai pas plus à ce sujet, car je pense que M. Etienne Wolff le traitera plus amplement dans une séance ultérieure.

L'exposé si attachant que nous a fait M. Prigogine tend à montrer qu'une hypothèse relevant de la physique théorique pourrait aider à interpréter ces faits de structuration progressive de la cellule-oeuf. S'il en était ainsi, cette manière de voir éclairerait sans doute aussi l'extraordinaire capacité de régulation, c'est à dire de réaction finalisée à certaines agressions, que possède l'oeuf jeune. Bien que l'on puisse tenter d'interpréter une telle régulation en restant sur le plan embryologique, ce serait un progrès remarquable que d'intégrer cette conception dans une théorie beaucoup plus vaste.

J. POLONSKY: Je crains que l'expression utilisée par M. Haken ne puisse conduire à une confusion. M. Haken a parlé d'une transformation de désordre en ordre et l'on pouvait en déduire que dans un laser, la transformation s'opère de cette manière. Je ne pense pas qu'il en soit ainsi. Il ne faut pas négliger, dans le cas du laser, l'ordre apporté par la source de pompage. Le laser fonctionne, en réalité, comme un convertisseur d'ordre où l'entropie négative d'inversion des populations est transformée en entropie négative de cohérence du faisceau laser.

Le laser transforme une distribution improbable d'états énergétiques en distribution improbable de phase. Je pense que M. Haken est d'accord avec moi sur ce point.

H. HAKEN: I will contradict your opinion because the pumping occurs completely incoherently that means that each individual atom is pumped completely differently from each other and in a random fashion. Nevertheless, in spite of this completely random process you find a completely coherent system.

S. L. SOBOLEV: Je voudrais faire une remarque visant les mathématiciens ici présents. Il est curieux que nous ne soyons liés apparemment ni avec les biologistes, ni avec les chimistes, alors que toute la science nous montre – dans de nombreux exemples – qu'avant toute découverte dans les sciences naturelles, la physique, la chimie etc., une nouvelle théorie mathématique s'était édifiée, provoquant une révolution générale dans toutes les disciplines. Mais il se passe un demi-siècle avant d'appliquer cette théorie nouvelle au développement de la science.

Les exemples? Je peux en fournir quelques-uns. Prenons l'histoire de la théorie de la relativité. C'est une géométrie non euclidienne, éclose au XIXème siècle, qui mena à cette théorie de la relativité, mais il se passa plus de cinquante ans avant que celle-ci vit le jour. Qu'il me suffise de citer les noms de Lobatchewsky, Diels, d'abord Riemann, ensuite Dale (le grand analyste Dale). Actuellement, les liens entre physique théorique et biologie se font à un niveau déjà bien connu, qui est celui de la physique quantique, peut-être de la physique classique, ou encore des équations aux dérivées partielles, dont nous a parlé M. Elsasser. Nous voici maintenant les témoins d'une nouvelle branche des mathématiques, la cybernétique, qui va engendrer des conceptions inédites, lesquelles à mon avis, bouleverseront la biologie et la science exacte, c'est-à-dire la physique et maintes disciplines. Que fait le physicien? Il applique tout ce qu'il sait à la biologie. C'est très bien. Mais cela suffit-il? J'en doute. Veuillez excuser cette petite critique à l'égard des physiciens.

Plusieurs orateurs, ont parlé de problèmes relativement nouveaux. C'est de la cybernétique. Mais je n'ai pas entendu évoquer, en la matière, de nouvelles découvertes qui pourraient féconder la biologie. Ce que nous attendons, nous mathématiciens, quand nous en parlons entre nous.

R. WURMSER: J'ai l'impression que les biologistes sont moins pessimistes que les physiciens dans leurs jugement sur la biologie. Par exemple, ils croient pouvoir établir des équations. J'entends par là qu'ils connaissent de très nombreuses lois quantitatives les unes statistiques, les autres portant sur des comportements individuels.

M. Dalcq rappelait tout-à-l'heure la complexité de la division cellulaire. Néanmoins il sait – et beaucoup mieux que moi – que l'on peut prévoir à une minute près dans des conditions précises les premiers stades de l'évolution d'un oeuf d'oursin fécondé et, avec une bonne approximation, la suite de son développement jusqu'à l'état de larve. Les neurophysiologistes savent provoquer à coup sûr le comportement de la faim, de la soif, du sommeil, en stimulant à l'aide d'une microélectrode un endroit précis du cerveau. Si bien que la position des biologistes est généralement différente de celle des physiciens. Ils sont les premiers à s'étonner de leurs prévisions étant donné qu'ils connaissent bien l'hétérogénéité essentielle du matériel vivant. C'est pourquoi ils recherchent des modèles mécaniques. Ils expliquent les choses par des templates, des surfaces complémentaires, des déformations, d'une manière générale par des agencements mécaniques, ceux-ci éliminant au maximum l'effet des bruits dus au désordre thermique. Tout au moins ils croient que cela leur est permis. Ils sont donc inquiets quand on leur démontre – ou qu'on essaye de leur démontrer – qu'ils ne devraient pas pouvoir faire des prévisions.

A. LICHNEROWICZ: Quel est leur problème alors?

R. WURMSER: Les biologistes s'efforcent de trouver des modèles, généralement mécaniques—comme je l'ai dit—mais qui ne sont pas des analogies naïves en ce sens qu'ils sont fondés sur les propriétés physicochimiques de mieux en mieux connues des biomolécules. Certaines difficultés que soulève l'application de la mécanique quantique ne sont pas réservées à la biologie.

Sauf aux confins de la neurophysiologie – touchant à la psychologie – où malgré des tentatives audacieuses existe encore trop d'inconnu – et en ce qui concerne l'origine de la vie, les biologistes croient comprendre dans une certaine limite ce qui se passe et que leurs modèles – est-ce une illusion? – ne sont pas contraires à la physique connue.

L. ROSENFELD: Oui, nous sommes d'accord.

A. FESSARD: Je suis aussi physiologiste. Donc, je fais partie de la famille des biologistes. Et je voudrais répondre brièvement à ce qu'a dit M. Wurmser.

Je crois qu'il y a deux catégories d'attitudes, et que l'on adhère soit à l'une soit à l'autre. Il y a l'attitude "réductionniste" – il me semble, M. Wurmser, que vous faites partie de cette catégorie . . .

R. WURMSER: Un peu . . . .

A. FESSARD: Et il y a ceux qui pensent que la physique d'aujourd'hui n'est pas capable d'expliquer tous les phénomènes de la Vie. Mais la physique actuelle

n'est pas une science terminée. Et si je ne suis pas moi-même réductionniste, c'est uniquement pour le présent. J'espère que la physique, qui a assez montré sa vitalité, se développera encore et nous révèlera de nouvelles lois.

S. L. SOBOLEV: Plutôt les mathématiques que la physique, je pense.

A. FESSARD: Oui. Quand je dis "physique", bien entendu, je pense aux cadres abstraits qui permettent à l'esprit humain de comprendre les phénomènes physiques; et, finalement, je conçois la physiologie comme une physique de l'être vivant, mais une physique qui est loin d'être à l'état de maturité où en est la physique mathématisable des phénomènes inorganiques.

L. ROSENFELD: Je me range plutôt du côté de M. Wurmser. Il me semble que la physique actuelle, disons la mécanique quantique, puisqu'il s'agit après tout de phénomènes moléculaires, est suffisamment bien établie pour que l'on puisse risquer, en tant que physicien, l'affirmation qu'elle doit suffire à rendre compte des mécanismes biologiques.

On sait, par les biologistes, que l'organisme est fait de composés moléculaires. On connaît l'ordre de grandeur des énergies en jeu, énergies chimiques même assez faibles; les mouvements ne sont pas très rapides. Donc on est dans les conditions de validité de la mécanique quantique, en laquelle on a confiance, car jusqu'à présent, dans tous les cas où on a tenté de l'appliquer, les résultats ont été satisfaisants. De ce point de vue, donc, aucune question de principe n'est soulevée. On ne demande pas de faire appel à des principes qu'on ignorerait encore. Pour prendre une analogie tirée de l'histoire de la physique: on connaît, depuis 1911, la superconductivité; on ne l'a comprise que tout récemment. Dans l'intervalle entre la connaissance de ce phénomène et la théorie qui enfin en rend compte, en remontant aux premiers principes de la théorie quantique, personne n'a jamais cru que l'on aurait à faire appel à un nouveau principe, encore inconnu.

Sommerfeld, je m'en souviens, citait la superconductivité comme la honte des physiciens, puisqu'ils étaient incapables de rendre compte du phénomène alors qu'ils avaient en main tous les éléments pour le faire. La raison pour laquelle cela a duré si longtemps est – comme on le comprend maintenant – que le phénomène présentait une complication d'un genre très particulier: un effet "coopératif", faisant intervenir un nombre d'éléments (d'électrons, dans ce cas) assez grand, mais non très grand. Et ce sont justement les systèmes composés d'un nombre "intermédiare" d'éléments qui sont les plus difficiles à traiter. Aux systèmes d'un très grand nombre d'éléments, on peut appliquer des méthodes statistiques bien développées. Les processus élémentaires, moléculaires, sont aussi accessibles, parce qu'ils ne comportent qu'un petit nombre de paramètres. Mais les phénomènes coopératifs dont nous parlons font intervenir un nombre de paramètres insuffisant pour l'emploi des méthodes statistiques, trop

grand cependant pour que les méthodes détaillées applicables à de très petits systèmes puissent être utilisées.

C'est plutôt là que je verrais l'origine de la grosse difficulté que nous avons à comprendre les phénomènes biologiques. C'est ce que M. Dalcq rappelait très justement: il ne faut pas se hâter de faire des généralisations, alors qu'on sait que l'on a affaire à un nombre considérable de facteurs, qui, probablement, jouent tous un rôle essentiel.

M. MARGENAU: I have hardly the right to claim your attention because I am here as a mere philosopher of science, not as an expert in biophysics. However, during this day of listening to various speakers, some questions have arisen in my mind, and since they are likely to have occurred to others, I would like to ask them in the hope of obtaining clarifications.

As a preamble to my inquiry, let me make a few pronouncements which will suggest my premises or, perhaps my prejudices. The issue of reducibility has recurred in our discussions. May I add that I believe that the circumstance that the phenomena of biology are in a measure explicable in terms of theories well known from physics and chemistry does not imply that new principles may not be required to understand them fully in the end. To make this evident let us start with classical quantum mechanics. To a certain extent we can comprehend the behavior of an assemblage of particles in terms of these basic laws. But we shall never understand thermodynamics without introducing *additional principles* concerning random phases, irreversibility, and so forth. In other words, as we pass from one level of complexity to a higher level of complexity two things seem to become necessary. One is to introduce concepts like temperature, phase, entropy, pressure and so forth which have no relevance whatever for individual particles. They become relevant only in a higher, more complex domain. Secondly, it has usually happened in the history of science that in these higher domains new laws need to be formulated which are applicable only to these higher-level phenomena but are never contradictory or even applicable on the lower levels. This may well be the situation as we pass from physics to biology.

Next I would like to say a few words about the relation between quantum mechanics and classical physics, a topic which was discussed a great deal this morning. Can we not agree that no classical theory of physics is acceptable if it contradicts the laws of quantum mechanics? In other words, do we not agree that quantal mechanics is the more general theory and that classical physics is a special case of it? Thus the question that was asked this morning concerns the relations between a logical system of larger range to one of smaller range; it has nothing to do with a change in basic epistemological relations.

Now my question: what is the magic of phases? The concept of phases has been injected into our discussions and invoked quite frequently as though the meaning of this term were clear. Many problems have been said to be resolved

by means of phases. The context has not always made clear to me whether the word stood for state of aggregation, for phase in the sense of phase space, or the renowned phases of the state function in quantum mechanics. My comments will refer only to the latter. There are clearly two ways of describing a complex biological system. One is in terms of pure states, of unique vectors in Hilbert space. Such a vector does, indeed, have a determinate phase, and this phase is, contrary to popular opinion, observable. But I see no relevance of it for biology at all. If it does have a significance, I should like to know what it is.

Secondly, composite phases appear when a pure state in Hilbert Space is compounded out of other states. A superposition of states in terms of a complete set of vectors involves phases of the individual vectors as well as resultant phases of the entire state. Here the individual phases are very important in determining physical effects, but again their significance for biology escapes me.

For in the first place the composition in question is entirely arbitrary and can be performed in an infinite number of ways. Hence I confront a difficulty. But there is a way of performing this composition which is based on the fact that an organism consists of a great number of individual parts. Each part has a quantum mechanical state, and the state of the total system may be written as a unique product of the Hilbert space of the individual parts. This is what Dr. Löwdin had in mind this afternoon, and the procedure is meaningful if one can suppose that the total organism is significantly made up of constitutent parts. It is a most fruitful approach in the simpler parts of chemistry.

The example chosen this morning was the superposition of the state of two hydrogen atoms to form what is called a bond. Now this is more or less all right. But, remember, this kind of superposition of individual parts into the state of a total system has meaning only if the total system is indeed in some sense separable. Separability does, in fact, prevail in the cases discussed this morning, in the superposition of hydrogen atoms as well as in the superposition of the states of assemblies of atoms and a light wave, i.e. the laser. These are proper examples only, however, because they permit us to start with an assumption of spatial separability as a good approximation. In a biological system the interactions between cells, and the parts of a cell, are largely unknown in their dynamical details, but are likely to be crucial and strong? Is this still a good approximation? It seems to me that there is a real likelihood that we may not describe an organism by means of a wave function that makes reference to individual constituent molecules and atoms.

There is one further point I should like to raise. It concerns phases in a complex state which in von Neumann terminology is represented by a mixture. Whether biological systems are mixtures or pure cases is, I think, a very interesting question, and it may indeed be relevant for our discussion. The issue here involves extremely difficult philosophical questions which touch upon such issues as the objectivity of quantum states, the theory of measurement, and indeed the theory of knowledge.

What troubles me is this. If the state of an organism is a quantum mixture, then the phases of the ingredient states are again not unique, for a mixture can be decomposed into pure states in a great many different ways (provided there is no degeneracy). The question as to which phases are important, therefore, raises its head again and I should be at a loss to answer it.

S. BRESLER: I have some questions connected with the lecture of Dr. Fröhlich. There were some statements, some predictions in this lecture which can be verified experimentally, but to try to find the phenomenon we need some estimation of its size, some estimation of the amplitude of oscillations of the electric field or the dipole moment. So I would ask Dr. Fröhlich if he can make an estimation of the order of magnitude of the effects.

A second thing which I find difficult to understand is what can be the generating system for such oscillations of frequency 10^{11} and even higher. The single source of energy in biology are chemical reactions and mainly the cleavage of ATP molecules. If you try to think of some specific times, say of the cleavage of a ATP molecule, you always come to frequencies which are six to seven powers less than 10^{11}. So I find it difficult to understand the mechanism of generation of such kind of oscillations.

H. HAKEN: I would like to make a comment on Dr. Margenau's comment with respect to the phases. I agree with the largest part you have said. But nevertheless I think in respect to phases I would like to avoid a misunderstanding.

In the laser we are not at all interested in the absolute phase of the laser light. In other words I agree with what you said, if you have a space vector in Hilbert space, you can choose any other state vector which has the same meaning. But what we are interested in in real life are correlations. An example is the correlation function $\langle b^*(t')b(t)\rangle$. Say we measure the light amplitude at a time t and later at a time t'. The absolute phase is unimportant but the relative phase is. That means we can choose any state vector here, but nevertheless the physics remains the same. Now comes a remark if the concept of coherence might be in some relation with biology or not. What does this mean?

If b at the time t' describes a process of very short memory then the b's are uncorrelated at all. What we find in biology is that living things retain their form or their function over very long time. Dr. Fröhlich's point of view was that we have phenomena which have a very slowly decaying phase. I think what we must look for is a model which explains us how we can understand that on the microscopic scale the things decay very fast in 10^{-8}s but on the macroscopic scale like the laser they decay only in minutes or hours. This is one of the problems. It may well be that what we are saying is completely irrelevant to biology but it also might direct biologists in further directions.

H. FRÖHLICH: I should like just to reply to Dr. Bresler. The first question is can we predict anything more definite as far as the frequency is concerned. We cannot, but we can notice that my range agrees with that mentioned by Dr. Careri for molecular frequencies. As far as the strength of the field is concerned one could indeed make a certain prediction but this would of course require some computation.

As I mentioned this morning a simple prediction can be made in the beginning when the processes are linear but when they become non-linear then one has to know quite a bit more about the surface tension of the cell and some other quantities. Since you were interested in these experiments I would be prepared to set up these calculations and give a definite answer. The second question I cannot answer, I know there must be a process which builds up just as for lasers but I do not know what it would be.

H. C. LONGUET-HIGGINS: I would like to follow up Dr. Margenau's point with what I regard as an even stronger argument for the irrelevance of the quantum-mechanical phase to the main problems of biology. Namely, when one describes a physical system by a wave function, or even by a density matrix, one must have an absolutely clear idea as to the physical boundaries of the system. It is very unclear to me what are the physical boundaries of an organism. For example, in trying to describe me would you include in your description the air which is in my lungs? The food which is now in my stomach, being digested? Because if you are in any doubt at all on these questions, you ought to be in very grave doubt about the possibility of describing me by a wave function. That is my first point.

Another point: If we *must* attempt to formalise the relation between quantum mechanics and the properties of living systems, let us use a Kubo type formalism rather than an elementary dynamical description, because all we can in fact do is to determine *correlations* between macroscopically observable quantities.

Now may I refer again to something that Dr. Tisza said. I regard it as exceedingly important, so perhaps he will forgive me if I repeat his point that there is a real problem in maintaining structural stability in an organism against thermal and quantum-mechanical fluctuations. His point was that this problem is in fact solved for us by the fact that one can separate two kinds of degrees of freedom from one another very well indeed. The fact that one can talk about benzene as benzene, or even of a particular benzene molecule as having a constant identity – even when it is under bombardment by other molecules – arises from the fact that no *electronic* transitions occur inside the molecule when it is knocked around fairly gently, though of course energy is transferred to and from other degrees of freedom. This seems to be the answer, formulated much more clearly than I ever heard before, to the question of how we can have, at the same time, highly random correlations in some degrees of freedom and highly persistent correlations

in the degrees of freedom that really matter, namely those that maintain the order of the atoms or groupings in large and elaborate biological molecules.

L. TISZA: It seems to me that the foregoing discussion suffers from an ambiguity surrounding the term "determinism" that is no less misleading for being sanctioned by general usage. The difficulty is closely related to the paradoxes of classical physics that I discussed. When people talk about determinism, they usually mean the temporal determinism of classical mechanics as it is actually observed in celestial mechanics. Yet in biology we have a determinism of a quite different sort; say, the development of the seed into the tree. A greatly simplified version of this process is found in the operation of a chemical factory. The two cases have very different qualitative properties. In the mechanical temporal determinism we have to rely on the exhaustive specification of the system, and this includes even the environment if there is any coupling between the two. Moreover, the system should not exhibit any dissipative mechanism leading to the loss of memory of the initial state. In contrast, in the chemical and the biological case the environment should satisfy only some very general requirements concerning the temperature, pressure and the proper supply of raw materials. Also the process is enhanced by a proper dissipative mechanism bringing about the loss of memory of the initial state: namely by stirring and other procedures that speed up the attainment of chemical equilibrium in each intermediate state of the chemical process. The lack of discrimination in the conceptual accounts of such different situations tends to produce conceptual confusion.

H. HAKEN: First of all I agree completely with you Dr. Longuet-Higgins that all we are saying from the physical side might be completely irrelevant for biology. What I would like to say is that in physics we have certain experiences and methods to explain them, for instance "feeding" lasers. One excites the laser all the time by a high flux of incoherent light that means you push the system all the time at random and nevertheless the laser light keeps its form. I think that's amazing, therefore I believe one should think a little bit of it.

L. ROSENFELD: I may perhaps say a few words in my defence. I may repeat, to begin with, what Dr. Haken has just said. It is quite possible that the models that we are discussing are not relevant. However we see general features in the biological phenomena which strongly remind us of those cooperative phenomena which we know in physics. Therefore it is natural to try and follow up this analogy. Now it is clear, as Dr. Fröhlich said, and well known to those who have looked into these phenomena, that the phase of the general wave function describing the system is of primary importance just for describing the correlations, and so it is natural to consider it.

It is quite possible that all the techniques that we have will prove insufficient

if we try to apply them to realistic models of biological organisms, but it may also prove that they will work, and I think that from the pragmatic point of view it is a constructive proposal to start with those methods which we know after all do work and to try them on new cases which we do not yet understand. That is the background for my foolhardy expectations.

R. P. DOU: I would like to comment on the possibility of a theoretical biology. I am a mathematician and will follow the line of Drs. Rosenfeld and Sobolev. I am not so optimistic as Dr. Rosenfeld. I do not think that we already know all the fundamental phenomena to construct a theoretical biology. I am also confident that in a short time biology will be formalized, as physics and as quantum theory have been formalized. Therefore we think that, starting from few axioms, theorems will be proved; or at least problems will be set, and when they are set soon afterwards will be solved. Theoretical biology will grow up as theoretical physics has grown up.

The question is whether the axioms we have from physics and chemistry are enough for explaining the formalizing of a fundamental theory of biology. I would rather think this is not the case. We need very much new phenomena. Not only new concepts, new theories for explaining the phenomena that we already know; but we need few phenomena and probably global phenomena, as mathematicians say, global phenomena, which may be quite independent of the sum of the phenomena of its parts. These phenomena are very difficult. The only way to get them will be just to try again and again. To study the biological processes. I am also not so optimistic as Dr. Sobolev that this time again mathematical theory will come before; perhaps it will come later. I do not know which will be the process, but something is needed very much. I think, in order to construct theoretical biology, it is important to get new axioms, and in order to find them, we have to understand new phenomena.

P. O. LÖWDIN: I would like to say to Dr. Margenau that I whole-heartedly agree with him when he explains his difficulties in understanding the nature of the "phases". Unfortunately, we don't get away from the problem. In classical mechanics, one has a Liouville-space based on the coordinates (x, p) and real functions, whereas, in quantum mechanics, one has an x-space (or a p-space) with complex wave functions which determine the probability distributions with respect to x and p. The physical situation is not fully determined unless we know the "phase" of the complex wave function.

In quantum statistics, the discussions are based on density matrices $\Gamma = \Gamma(x|x')$ instead of wave functions $\Psi = \Psi(x)$, but the phase problem persists. The diagonal elements $\Gamma(x|x)$ of the density matrix are, of course, independent of the phase, but, unfortunately, one needs also the non-diagonal elements $\Gamma(x|x')$ for $x \neq x'$ in the theory, and they are difficult to understand. However, I don't agree with

Dr. Longuet–Higgins that the phases are irrelevant in biology, since it would mean that one would throw away all aspects of the chemical bond. One would not be able to distinguish between bonding orbitals, say $(a+b)$, and non-bonding orbitals, say $(a-b)$, and the entire molecular-orbital approach would have to be abandoned.

H. C. LONGUET–HIGGINS: I speak of very large systems.

P. O. LÖWDIN: For large systems of random-phase character, I would agree with you, but I believe that the situation is different for the highly organized systems in the cells. The phase rule

$$\alpha = \frac{2\pi}{h}(px - Et),$$

given by Louis de Broglie in 1924 forms a very good starting point for studying phases of free particles, the stationary states have usually well-determined phases (except for some irrelevant constant), but one has otherwise little definite instructions how to "measure" a phase for a manyparticle system.

B. B. LLOYD: I have a question for Dr. Fröhlich. He made a prediction from his proposed longitudinal oscillations in which he dealt with the question of the concentration of cells and the distance between the cells, and the effect that these might have on cell-growth. Now if I got it correctly, you suggested that the cells have to be far apart, and that when they divide and increase in number they come closer together, so that these special forces would cease to operate and cell division would tend to cease. As far as I know, the concentration of cells in a very young organism such as a foetus is the same as in you and me, but the cell of course divides quite happily in the foetus, and much more than in adults like you and me, although it is quite true that we both have cell systems which are dividing quite rapidly, for example in the skin and in the bone marrow. Once again both these sets of cells are highly concentrated and as concentrated as in those regions of the body where no division is taking place. The advantages of your model are that they do immediately imply some sort of observational or experimental test; but when the test is applied, it is on the whole against the model.

G. CARERI: As a physicist, I would like to ask the biologists whether there is any evidence of long range effects inside a cell between cell subunits. There are certainly chemical effects which I call first neighbour effects; one molecule acts on the next one, possibly this one on the next one again, and even feedback is possible if there is some circular arrangement of molecules, as is well known from enzymatic reactions for instance. So far for short range effects. Now the point is this. Is there any evidence pro and contra the existence of long range effects (effects that propagate at large distances)? If these do exist, I do not know any

other way of explaining them than by the electromagnetic field, and in that case you must have a window in the polarizability of water. Whenever I ask a biochemist, he replies usually that short range effects explain everything. But chemists explain everything in terms of chemistry, I am afraid. I would really like to have this question settled experimentally by biologists: is there anything that cannot be explained purely by short range effects? I hope one day you may give us the answer; this would be an immense benefit for us.

M. DALCQ: A l'intéressante question de notre Collègue, je crois pouvoir répondre que, dans l'ontogenèse, on connaît certaines manifestations qui sont préparées très tôt et restent longuement latentes. Le cas le plus frappant concerne l'apparition de la lignée germinale. Les belles recherches de feu M. Bounoure sur les Amphibiens ont montré que les gonocytes primordiaux dérivent des cellules de la gastrula qui ont reçu un matériel, le déterminant génital, décelable au pôle végétatif de l'oeuf récemment fécondé. Cette notion vient encore de faire l'objet d'une confirmation basée sur l'instillation d'un isotope dans le déterminant. Entre l'apparition de celui-ci et celle des gonocytes, il s'écoule plusieurs dizaines d'heures. On pourrait encore invoquer d'autres faits relatifs d'une part aux Mammifères et d'autre part à des résultats de l'hybridation moléculaire, mais j'ai l'impression que ma réponse ne répond pas effectivement à la préoccupation de notre Collègue?

G. CARERI: Ce que je disais visait seulement la cellule et non un organisme où la chose peut être trop compliquée pour moi.

S. BRESLER: Une petite observation: quand vous avez beaucoup de chromosomes, séparés par des distances microscopiques de l'ordre de grandeur du micron, ils arrivent à se retrouver pendant la méiose et de façon très détaillée. C'est une juxtaposition qui se passe. Les gènes, même les points homologues, arrivent à se retrouver deux à deux. Ici, il doit y avoir un rapport, à mon avis, avec les forces à longue distance. Je ne sais pas d'autre forces moléculaires à longue portée que les forces de Coulomb. Et ces forces peuvent être specifiques pour des résaux compliqués de charges. Je crois que c'est l'exemple le plus courant, indiquant que la cellule redispose de forces, qu'on peut expliquer, en détail, comme étant à longue portée.

Directeur de la publication: M. Maurice MAROIS
Imprimé en Hollande