Long-Range Coherence in Biological Systems (*).

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1. – Introduction.

The great success of molecular biology arises from the discovery of the detailed structure of biomolecules such as DNA and enzymes. No systematic spacial order was found, and it was concluded that these molecules do not possess a physical order. Physical order, however, does not express itself in spacial order only. Thus superfluid helium, or the electrons in a superconductor exhibit an order that might be termed « motional order ». This type of order is connected with the existence of macroscopic wave functions, which implies the existence of certain quantum phase correlations over macroscopic distances or the existence of coherent states.

Other correlations connected with the phase of oscillating systems rather than with those of macroscopic wave functions are also well known when those systems are lifted from their thermal equilibrium. A well-known example are laser systems which need not exhibit a spacial order as, *e.g.*, in the case of gas lasers.

Many other types of physical order may be imposed on certain systems

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when they are lifted from their thermal-equilibrium state even though they are spacially disordered. This does not hold, however, for all systems, and no general criterium has been found, so far, which when satisfied permits particular systems to exhibit some type of order when energy is supplied to them. Most systems, however, simply raise their temperature.

Biological materials, when they exhibit typical biological properties, must be « fed », *i.e.* energy passes through them. This energy may arise from chemical processes, or it may be supplied by the Sun.

It seems rash, therefore, to conclude from the absence of spacial order —obtained from structural analysis—that no physical order exists in biological systems. On the contrary, it has been suggested several years ago that they belong to those systems in which the supply of energy imposes a characteristic order [1, 2].

In approaching these questions from the point of view of theoretical physics it must be realized that, in contrast to most materials usually treated in physics, biological materials have been selected through long evolutionary processes. As a consequence, they often show quite extraordinary properties, and, rather than ask whether some material properties seem likely, one should ask whether they are possible. Clearly, in the first place, the role of theoretical physics must be to decide what questions should be asked; subsequent developments should then work in close contact with experiments.

It has often been thought that exact knowledge of the atomic structure of a system will provide all answers at least in principle. This is already a basic mistake [3], even in the case of the physics of simple systems. Thus, for example, the above-mentioned concept of macroscopic wave function refers to the whole assembly of particles, *i.e.* it is a collective property which cannot in a simple way be reduced to properties of individual particles.

2. – General.

In looking for a striking material property common to most biological systems one will, no doubt, choose their dielectric properties [1, 2, 4]. Biological systems are, of course, not uniform, but composed of many different such systems. In ordinary physics, one would then extract each subsystem, *e.g.* a certain type of molecule, and determine its dielectric properties, *e.g.* its dipole moment. In solution this dipole moment, say μ_i, would be slightly different from the moment μ_v in vacuum owing to polarization effects. Such a procedure would be highly misleading in the biological case, say for water-soluble proteins. Their conformation is largely dominated by the interaction of their charged groups with the surrounding water and ions which thus form an integral part of the structure and hence of the measured dipole moment. Under these circumstances, very high internal electric fields may exist in such systems.

Most striking, of course, are the fields in cell membranes which have average values of the order of 10^5 V/cm, which in ordinary materials would require great precautions to avoid breakdown. Inhomogeneous regions, *e.g.* through proteins dissolved in the membrane, might lead to much higher local fields. These fields play a basic role in nerve conduction, but here weaker fields could fulfil the same purpose. Their role in the membranes of other cells is unknown.

One notices that the energy difference of a unit electronic charge across the membrane (about 10^{-6} cm) would, at room temperature T, amount to about $3kT$. This suggests that the transport of single charges obtains a significance against thermal noise.

Also in a field $F \sim 10^5$ V/cm the energy μF is larger than kT when μ is the dipole moment of a small protein, say $\mu \sim 300$ Debye units. This suggests that proteins dissolved in membranes are oriented by the field.

In addition, however, the whole membrane system is strongly polarized by the field. As a consequence, an oscillation of a section of the membrane—or of certain proteins dissolved in it—is connected with a corresponding electric vibration, so that the longest electric wave usually yields an electric-dipole vibration. According to one of our main suggestions, such vibrations are very strongly, coherently, excited in biological systems when they are active, *i.e.* when metabolic energy is available.

Now it must be realized that the displacement of a single ion by 10^{-6} cm produces a very large dipole moment of the order of 500 Debye units. It would be wrong, however, to neglect other processes arising from such displacements, for the change of electric field arising from this displacements may substantially alter the polarization in the neighbourhood of the ion (note that the electric field at a $3 \cdot 10^{-7}$ cm distance from the electronic charge is of the order of 10^6 V/cm) and cause other ions to move. Under these circumstances, one would expect such displacements to become stabilized, and our second principal suggestion states that biological systems have metastable states with very high electric polarization.

How can one support theoretically such general statements referring to a variety of complicated materials? It is already clear from the above that we are dealing with strongly nonlinear effects. This provides possibilities only occasionally contemplated in ordinary physics. Our method will be to formulate simple, but general models which do show the required properties. General conditions required in these models then impose corresponding conditions on the respective biological systems. If experiments confirm the theoretical predictions, then we can conclude that the molecular evolution has led to the selection of materials with the required properties. This does not imply that other systems do not exist which do not have the required properties, though from a structural point of view they could be very similar to the systems which

do have these properties. The difference between the two would then rest in their nonlinear behaviour, *i.e.* in properties of certain excited states which would not be revealed in structural analysis.

3. – The vibrational model.

Any system containing charged particles is capable of long-wave electrical vibrations. Such a system need not be homogeneous. One of the characteristics of these vibrations is the existence of a lowest frequency $\omega_1/2\pi$, different from zero. Our system is assumed to possess such modes, $\omega_1, \omega_2, \ldots, \omega_z$. They are considered not to interact with each other, but to be strongly coupled to the surroundings, *i.e.* to the other modes of the systems which will be treated as a heat bath at temperature T. Let n_k be the number of quanta $\hbar\omega_k$ in the mode ω_k. Then, through first-order processes, single quanta $\hbar\omega_k$ may be emitted to or absorbed from the heat bath, so that the rate of change $\dot{n}_{k,1}$ of n_k due to these processes is [2, 5]

$$\dot{n}_{k,1} = -\varphi\big(n_k \exp[\beta\hbar\omega_k] - (n_k + 1)\big)\,, \tag{3.1}$$

where $\beta = 1/kT$, and φ will depend on T and, in general, also on ω_k. For simplicity we shall neglect the ω_k-dependence. The ratio of emission to absorption processes is governed by detailed balance.

Similarly, for second-order processes we find

$$\dot{n}_{k,2} = -\chi \sum_j \big(n_k(1 + n_j) \exp[\beta\hbar\omega_k] - n_j(1 + n_k) \exp[\beta\hbar\omega_j]\big)\,. \tag{3.2}$$

Again, apart from depending on T, the transition probability χ could depend on k and j, but we shall neglect this. This will greatly simplify the calculations, but should have no influence on the main results.

We note that, on this choice,

$$\sum_k \dot{n}_{k,2} = 0\,, \tag{3.3}$$

i.e. such processes lead to interchange of quanta $\hbar\omega_k$ without alteration of their total number.

Now we consider that energy is supplied at the rate s_k to the mode ω_k. We then find, for the total rate of change $\dot{n}_k$,

$$\dot{n}_k = s_k - \varphi\big(n_k \exp[\beta\hbar\omega_k] - (n_k + 1)\big) - \\ - \chi \sum_j \big(n_k(1 + n_j) \exp[\beta\hbar\omega_k] - n_j(1 + n_k) \exp[\beta\hbar\omega_j]\big)\,. \tag{3.4}$$

We wish to solve this equation for the stationary case, *i.e.* when

$$\dot{n}_k = 0 \,. \tag{3.5}$$

We may derive the general behaviour of n_k in a simple manner, though it would be difficult to solve this system of quadratic equations exactly.

Summation over k with the definition

$$S = \sum s_k \tag{3.6}$$

yields

$$S = \varphi \sum_k \left(n_k \exp\left[\beta\hbar\omega_k\right] - (n_k + 1)\right) . \tag{3.7}$$

Introducing the total number of quanta N,

$$N = \sum n_k \,, \tag{3.8}$$

we find with

$$\omega_1 \leqslant \omega_k \leqslant \omega_z \tag{3.9}$$

that $\left(\text{note } \sum_k 1 = z\right)$

$$N\left(\exp\left[\beta\hbar\omega_z\right] - 1\right) > S/\varphi + z > N\left(\exp\left[\beta\hbar\omega_1\right] - 1\right) . \tag{3.10}$$

This means that N must increase proportional to S if the supply S is sufficiently large.

Now define μ by

$$\exp\left[-\beta\mu\right] = \frac{\varphi + \chi \sum (1 + n_j)}{\varphi + \chi \sum n_j \exp\left[\beta k\omega_j\right]} , \tag{3.11}$$

so that

$$1 - \exp\left[-\beta\mu\right] = \frac{\chi \sum \left(n_j \exp\left[\beta\hbar\omega_j\right] - (1 + n_j)\right)}{\varphi + \chi \sum n_j \exp\left[\beta\hbar\omega_j\right]} . \tag{3.12}$$

From (3.7) it then follows that

$$\mu \geqslant 0 \tag{3.13}$$

and

$$1 - \exp\left[-\mu\beta\right] = \frac{\chi}{\varphi} \frac{S}{\varphi + \chi \sum n_j \exp\left[\beta\hbar\omega_j\right]} \geqslant 0 . \tag{3.14}$$

Equation (3.4) with (3.5) can thus be formally solved by

$$n_k = \left(1 + \frac{\varphi}{\chi} \frac{s_k}{S} \left(1 - \exp\left[-\beta\mu\right]\right)\right) \frac{1}{\exp\left[\beta(\hbar\omega_k - \mu)\right] - 1} , \tag{3.15}$$

and $n_k \geqslant 0$ together with (3.13) yields

$$\hbar\omega_1 > \mu \geqslant 0 \,. \tag{3.16}$$

This inequality permits the establishment of an upper limit for N although μ is a complicated function of all the n_k. For (3.15) then yields

$$N = \sum n_k < \left(1 + \frac{s_m(1 - \exp[-\beta\hbar\omega_1])\,\varphi}{\chi S}\right) \sum_k \frac{1}{\exp[\beta(\hbar\omega_k - \mu)] - 1}\,, \tag{3.17}$$

where s_m is the largest of the s_k.

Clearly, if the sum in (3.17) can be replaced by an integral, then for $\mu \sim \hbar\omega_1$ a value independent of the s_k will be reached. Moreover, always $s_m/S \leqslant 1$, so that an upper limit for N independent of S is obtained. This contradicts the conclusion drawn from (3.10), according to which N must increase proportional to S if S is sufficiently large. This situation is the same as normally found in Einstein condensation of a Bose gas. Thus the replacement of the sum by an integral is incorrect; μ takes a value close to $\hbar\omega_1$ such that n_1 becomes very much larger that all the other n_k.

It follows then that a single mode ω_1 gets very strongly (coherently) excited when the energy supply is larger than a critical one.

As special cases we may consider that all s_k are equal. Then

$$s_k/S = 1/z \tag{3.18}$$

and (3.15) becomes

$$n_k = \left(1 + \frac{\varphi}{\chi_z}\left(1 - \exp[-\beta\mu]\right)\right) \frac{1}{\exp[\beta(\hbar\omega_k - \mu)] - 1}\,. \tag{3.19}$$

As another extreme consider that all s_k vanish except for $k = k_0$.

Then

$$s_k = S\delta_{k,k_0}\,, \qquad s_{k_0} = S \tag{3.20}$$

and

$$n_k = \left(1 + \delta_{k,k_0}(1 - \exp[-\beta\mu])\,\frac{\varphi}{\chi}\right) \frac{1}{\exp[\beta(\hbar\omega_k - \mu)] - 1}\,. \tag{3.21}$$

To understand qualitatively these conclusions, we notice first of all that the case $\chi = 0$ leads to a completely trivial result, namely

$$n_k = \left(1 + \frac{s_k}{\varphi}\right) \frac{1}{\exp[\beta\hbar\omega_k] - 1}\,, \qquad \text{if } \chi = 0\,, \tag{3.22}$$

i.e. to a modified thermal-equilibrium Planck distribution. It will be noticed from (3.11) that $\chi = 0$ in fact entails $\mu = 0$ and thus eliminates the occurrence of Bose condensation. Thus the nonlinear terms χ arising from a strong interaction with the heat bath tend to force the system into a thermal-equilibrium distribution making use of a chemical potential μ.

A main difference from ordinary condensation of a Bose gas in thermal equilibrium should also be noted. There the ordered (condensed) state is reached by lowering the temperature. In our case, the ordered state is reached by supplying sufficient external energy to the system. Quite a similar situation prevails with respect to the second of our concepts (sect. **4**).

The above model, naturally, is a very simplified version of any actual situation. It has a very general consequence which might not depend on modifications required in particular cases, namely the coherent excitation of a polar mode when energy supply exceeds a critical magnitude.

Which frequencies should we anticipate? Roughly speaking, if a polarized system of linear dimensions l carries out long-wave elastic vibrations (*e.g.* breathing vibrations), then the electric polarization of the system implies coexistence of an electric-polarization vibration with the same frequency

$$\nu \sim v/l\,, \tag{3.23}$$

where v depends on the elastic constants and can formally be expressed as a velocity of sound. Thus $l = 10^{-6}$ cm and $v = 10^5$ cm/s would yield $\nu = 10^{11}$ Hz, but $l = 3 \cdot 10^{-7}$ cm (small protein) with $v = \frac{1}{3} 10^5$ cm/s yields, of course, the same value. The band of polarization waves ω_k would then consist of the interacting vibrations of such units, and also of higher vibrational states of the same unit. It must be emphasized again that the existence of long polarization waves does not require homogeneous material.

A further condition is the absence of unduly high friction, which probably will mean that surfaces facing water should not move. This does not hold, however, for structured water, which is to be considered as an integral part of the particular biological unit. Most likely, these conditions are satisfied by proteins in or near membranes. Thus, if $\Delta\nu$ is the frequency width, we have in this case

$$\nu \sim 10^{11}\ \mathrm{Hz}\,, \qquad \frac{\Delta\nu}{\nu} \ll 1\,, \qquad s > s_0 \tag{3.24}$$

as condition for the excitation of coherent vibrations. Here s is an appropriate average over the rate of energy supply and s_0 is the threshold value for Bose condensation.

It should be emphasized that other frequencies, both higher and lower, are well feasible. Thus larger units such as DNA-protein complexes might

well possess lower frequencies. Higher ones, on the other hand, may be based on a combination of the various rotational and vibrational subgroups of relevant molecules.

4. – The high-polarization model.

Consider [6] a polarizable material, polarization P. Its mean « self-energy » can then be written as $\frac{1}{2}a^2\overline{P^2}$, where the bar indicates an appropriate average and the positive a^2 depends on the polarizability, including size and shape of the material. These definite size and shape imply the elastic energy of the material to be a minimum relative to small deformations. If these are measured in terms of a deformation parameter η, then on deformation the elastic energy increases by $\frac{1}{2}\eta^2\varepsilon$, where $\varepsilon > 0$ depends on the elastic properties. In the case of a sphere, for instance, the deformation could produce an ellipsoid with eccentricity η. Now the polarizability in general is not an extremum at $\eta = 0$, so that a^2 would have to be replaced by $a^2(1 + c\eta)$, where c may be positive or negative. The total contribution to the free energy thus amounts to

$$U = \tfrac{1}{2}a^2(1 + c\eta)\,\overline{P^2} + \tfrac{1}{2}\eta^2\varepsilon\,. \tag{4.1}$$

Minimizing with regard to η at fixed $\overline{P^2}$ yields

$$\eta = -\frac{1}{2}\frac{ca^2}{\varepsilon}\,\overline{P^2}, \tag{4.2}$$

so that

$$U = \frac{1}{2}a^2\,\overline{P^2}\left(1 - \frac{1}{4}\frac{c^2}{\varepsilon}a^2\,\overline{P^2}\right). \tag{4.3}$$

Thus increasing $\overline{P^2}$ ultimately may lead to decreasing U. At this stage, the linear approximation η and the quadratic one in P will probably have become invalid. Higher-order terms may thus reverse this trend and lead to a minimum of U at a certain $\overline{P^2}$. If U at this value is negative, then the material would acquire a spontaneous dipole moment. If U is positive, then a metastable state with spontaneous polarization exists.

These conclusions are of a very general nature. They follows from the shape dependence of the polarizability and require the material to be sufficiently soft, *i.e.* ε should be sufficiently small.

They can be extended to a dynamical model composed of a polarization field $\boldsymbol{P}$ and an elastic (acoustic) field $\boldsymbol{A}$. Let ω_0 be the circular frequency of long-wave polarization waves in the absence of any interaction with the elastic field, then with such an interaction the density of potential energy has the

form

$$W = \tfrac{1}{2}\omega_0^2 \boldsymbol{P}^2 + \left(\tfrac{1}{2}v^2(\operatorname{div}\boldsymbol{A})^2 + c\boldsymbol{P}^2 \operatorname{div}\boldsymbol{A}\right)(1 - d^2\boldsymbol{P}^2)\,, \tag{4.4}$$

where v is the velocity of sound, d^2P^2 is an *ad hoc* term introduced to achieve stabilization for high P^2.

Note that, for long waves,

$$\varrho = \operatorname{div}\boldsymbol{A} \tag{4.5}$$

may be introduced as change in density. The static case requires minimization of (4.4) with regard to ϱ and P^2, so that for homogeneous displacements

$$\varrho = -\frac{cP^2}{v^2}\,, \tag{4.6}$$

yielding

$$W = \frac{1}{2}\omega_0^2 P^2 - \frac{1}{2}\frac{c^2}{v^2}(1 - d^2P^2)\,. \tag{4.7}$$

Apart from the different notation, this result corresponds to (4.3) except that the d^2P^2 term leads to a stabilization at high P^2.

Now we can introduce the density of kinetic energy

$$K = \tfrac{1}{2}(\dot{\boldsymbol{P}}^2 + \dot{\boldsymbol{A}}^2) \tag{4.8}$$

and hence from the Lagrangian density L obtain the equations of motion in the usual way,

$$\delta\int L\,\mathrm{d}^3\boldsymbol{r}\,\mathrm{d}t = \delta\int (K - W)\,\mathrm{d}^3\boldsymbol{r}\,\mathrm{d}t = 0\,, \tag{4.9}$$

where $\boldsymbol{r}$ is the space vector and t the time. The assumption that acoustic phonons are absent then permits the elimination of the $\boldsymbol{A}$-field and yields an equation of motion of the form

$$\ddot{\boldsymbol{P}} + \frac{\partial V(P)}{\partial \boldsymbol{P}} = 0\,. \tag{4.10}$$

The effective potential $V(P)$ has the form

$$V(P) = A + BP^2 + CP^4\,, \tag{4.11}$$

apparently a harmless anharmonic oscillator. This is misleading, however, for the coefficients A, B, C depend on the mean square amplitude

$$p = \overline{P^2}\,, \tag{4.12}$$

such that

$$A = \frac{1}{2}\frac{c^2}{v^2}p^2, \tag{4.13}$$

$$B = \frac{1}{2}\left(\omega_0^2 - 2\frac{c^2}{v^2}p - \frac{d^2c^2}{v^2}p^2\right), \tag{4.14}$$

$$C = \frac{c^2d^2}{v^2}p\,. \tag{4.15}$$

For small p clearly the CP^4 term is negligible and B becomes $\omega_0^2/2$, so that an harmonic oscillation with frequency ω_0 is obtained.

For increasing p, however, the magnitude of B decreases, *i.e.* the mode softens. For appropriate values of the parameters it is then found that a metastable state with permanent polarization $\pm P_0$ exists and that the system has two branches of oscillation: one around $P = 0$ and another with limited amplitude around $\pm P_0$. In this case, the effective potential $V(P)$ has a maximum at $P = 0$ and two minima at $P = \pm P_0$. The value of P_0 is found by minimizing (4.7), which yields

$$P_0^2 = p_0 = \frac{1}{3d^2}\left(1 + \sqrt{1-\lambda}\right), \tag{4.16}$$

where

$$\lambda = \frac{3v^2d^2\omega_0^2}{c^2}. \tag{4.17}$$

Thus $\lambda < 1$ is a necessary condition for the existence of a P_0, and it can be shown that this state is metastable, *i.e.* has positive energy when

$$\frac{3}{4} < \lambda < 1\,. \tag{4.18}$$

For $\lambda < \frac{3}{4}$ its energy is negative, *i.e.* it becomes the (ferroelectric) ground state.

We notice again that small v^2, *i.e.* softness of the material, favours the establishment of a polarized state. We also note that in many ferroelectric materials the effective potential has a minimum at $P = 0$ at high temperatures. The mode softens as we decrease the temperature towards the Curie point and below we find two minima at $P \pm P_0$.

In our case $V(P)$ has its minimum at $P = 0$ at low energies, but supply of energy may establish the quasi-ferroelectric state with minima at $P = \pm P_0$. Thus here as in the case of sect. **3** a long-range order—coherent vibrations, or permanent polarization—is established through the supply of energy.

Clearly actual biological materials will behave in a much more complex way than discussed in this simple model. We should recall in this case that structured water and various ions are to be considered as an integral part of the system.

This implies considerably higher nonlinear effects than discussed above. While these will have to be treated case by case, it seems that they usually will contribute to the stabilization of our metastable state. Thus a polarized molecule will shift mobile ions so that its energy is lowered; in turn, this will, of course, affect the magnitude of polarization.

5. – General consequences.

The two types of excitation discussed in sect. **3** and **4** can have far-reaching biological consequences. First of all, it should be noticed that they require supply of energy, *i.e.* activation. Both can then lead to forces which were absent before activation, and to storage and transport of energy.

Cell water contains considerable amounts of small ions which tend to screen any static electric charges at short range. Hence a system activated to a high dipole moment (sect. **4**), *e.g.* a protein, may exert considerable forces in water-free regions, but will be screened for long-range interaction. This screening does not hold, however, for an oscillating field at frequencies of the order of 10^{11} Hz (sect. **3**). Thus, if the coherently excited vibration represents an oscillating giant dipole, then long-range forces may be activated. They will be shown to be frequency selective.

Consider two oscillating giant dipoles at distance R with frequencies ω_e and ω_s, respectively, in the absence of interaction [4, 7]. At sufficient distance, their interaction is essentially dipolar, since other interactions decrease much more rapidly with R. The combined system then has two normal modes ω_+, ω_-, where

$$\omega_\pm^2 = \tfrac{1}{2}(\omega_e^2 + \omega_s^2)\left(1 \pm (q^2 + Q^2)^{\frac{1}{2}}\right). \tag{5.1}$$

Here (by assuming $\omega_e^2 \geqslant \omega_s^2$)

$$q = \frac{\omega_e^2 - \omega_s^2}{\omega_e^2 + \omega_s^2} > 0 \tag{5.2}$$

and Q essentially is the ratio of the interaction energy between the two giant dipoles and their internal potential energies.

It thus depends on the distance as $1/R^3$.

In the particular case that the giant-dipole oscillations in the two molecules consist in correlated oscillations of, respectively, z_e and z_s elastically bound ions of charge e and of equal mass M, then

$$Q = \gamma e^2 (z_e z_s)^{\frac{1}{2}} / M R^3 (\omega_e^2 + \omega_s^2), \tag{5.3}$$

where γ is a numerical constant.

Clearly the expression for ω_-^2 holds only when $\omega_-^2 > 0$; at short distance thus mode softening occurs.

The interaction energy I is defined as the difference of the free energy F at distance R from its value at $R \to \infty$. Now consider the case that the state with the lower frequency has been coherently excited (n_- quanta) so that the contribution of ω_+ to F can be neglected. Then

$$I = F(R) - F(\infty) = n_- \hbar(\omega_-(R) - \omega_-(\infty)) = \tag{5.4}$$

$$= \frac{1}{\sqrt{2}} n_- \hbar(\omega_e^2 + \omega_s^2)^{\frac{1}{2}} \left\{(1 - \sqrt{q^2 + Q^2})^{\frac{1}{2}} - (1 - q)^{\frac{1}{2}}\right\}.$$

This energy is always negative, *i.e.* attractive. Furthermore, if $\omega_e \neq \omega_s$, then at sufficient distance $Q^2 < q^2$ and we find, after development,

$$I = -\frac{\hbar n_-}{4\sqrt{2}} (\omega_e^2 + \omega_s^2)^{\frac{1}{2}} \frac{Q^2}{q(1-q)^{\frac{1}{2}}} \propto -\frac{1}{R^6}. \tag{5.5}$$

If, however, $\omega_e^2 \simeq \omega_s^2$ and $Q^2 \gg q^2$, $q^2 \ll 1$, then

$$I \simeq -\frac{\hbar n_-}{\sqrt{2}} (\omega_e^2 + \omega_s^2)^{\frac{1}{2}} Q = -\frac{\hbar n_-}{\sqrt{2}} \frac{\gamma e^2 (z_e z_s)^{\frac{1}{2}}}{M(\omega_e^2 + \omega_s^2)^{\frac{1}{2}}} \frac{1}{R^3} \propto -\frac{1}{R^3}. \tag{5.6}$$

In this case of near resonance, the always attractive interaction has very long range. Roughly, if

$$U = \hbar n_- \omega_e \tag{5.7}$$

is the energy of excitation, using $\omega_e \simeq \omega_s$, we have

$$I \simeq - U \frac{e^2 (z_e z_s)^{\frac{1}{2}}}{M \omega_e^2 R^3}. \tag{5.8}$$

While thus activation of coherent vibrations may lead to long-range, frequency-selective interaction, activation of the polar state leads to short-range nonselective forces which might facilitate transport of ions within the particular material, or across it.

Long-range selective forces may lead to selective transportation of molecules like enzymes and thus initiate a particular trend of chemical events. It might also be relevant for the transportation of larger units.

It has been suggested that these properties are an essential feature in the high catalytic power of enzymes [4, 6, 8]. Thus the high internal fields arising from the strongly polarized state could reduce activation energies, while excitation of coherent modes could be used for the transport of energy.

Independently [9], the same conclusion has been reached from an analysis of a great variety of enzymatic reactions.

In [10] it has been suggested that the selective long-range interaction (sect. **3**) may be responsible for the attraction of a homologous pair of chromosomes in meiosis—an interaction which according to [11] has till then remained « a great mystery ».

A number of other possible consequences has been discussed elsewhere [1, 2, 4, 12].

Selective long-range interaction in conjunction with the existence of highly polar metastable states may also be decisive for the establishment of the well-known low-frequency electric vibrations in the brain, whose biological significance is only now being explored [13]. It has been shown that the long-range coherent interaction (based on the 10^{11} Hz coherent vibrations) could in an enzyme-substrate system lead to collective enzymatic reactions resulting in slowly varying (periodic) excitation and de-excitation of the system of enzymes from the only slightly polar ground state into the highly polar metastable state. Thus a slow chemical oscillation is connected with a corresponding electric vibration. The strong electric interaction between the highly polar states in conjunction with the considerable damping of electric currents then imposes on them a limit cycle condition, which recently has been investigated [14]. This model requires large regions to oscillate coherently as has actually been found [15].

6. – Experimental evidence.

In active biological systems experimental evidence for the existence of coherent electric oscillations in the 10^{11} Hz region would require methods which have not yet been fully developed (cf., however, Note added in proofs). Evidence does exist, however, that radiation in this frequency region may have very strong effects on such systems. The most comprehensive report on such effects has been presented in a meeting of the USSR Academy of Science [16]. Properties of a great variety of objects have been found to be strongly influenced by coherent electromagnetic waves in the $(5 \div 7)$ mm (vacuum) wave-length region. Almost all experimental results have in common:

i) That they very strongly depend on frequency in a region in which the optical constants have the appearance of broad bands; often the biological effects showed typical resonance character.

ii) The dependence on intensity exhibits a threshold below which no biological effects occur and above which they are nearly independent of intensity.

To interpret these results [17], we assume that these biological effects are initiated by a first step which is sensitive to a radiation followed by a chain of other possibly very complicated effects which are insensitive to it. The

first step might be connected with a long-range interaction arising from coherent excitation of a molecule, *e.g.* an enzyme which could be attracted to its substrate. Let the time required for this be $t_1(s)$, where s represents the radiative supply of energy to it. According to sect. **3**, excitation of the coherent mode requires a threshold s_0. With growing s ($> s_0$) the time $t_1(s)$ will decrease, so that the total time for the whole process

$$t = t_1(s) + t_2 \to t_2 \tag{6.1}$$

will approach the s-independent time t_2 required for the s-independent chain of further biological steps. Thus in these experiments we find

$$\nu \sim \frac{1}{2} 10^{11}\,\mathrm{Hz}\,, \qquad \frac{\Delta\nu}{\nu} \ll 1\,, \qquad s > s_0\,, \tag{6.2}$$

as predicted in (3.24).

We note that the resonancelike frequency dependence in a region in which the optical constants show little frequency dependence is the best proof that we are not dealing with thermal effects.

The magnitude of s_0 has been estimated theoretically [18] from calculations using methods of laser physics and found of the order 0.04 mW/cm², which agrees with some of the experimental results (*).

The Russian experiments range from various effects on bacteria, growth of yeast cultures, influence on human and animal cells to effects on various genetic properties. Depending on the type of process stimulated by the radiation, a certain biological activity might be increased or decreased. Independently, on a smaller scale and without extensive frequency resolution, biological effects near $0.7 \cdot 10^{11}$ Hz and $1.4 \cdot 10^{11}$ Hz have been found by other investigators [19, 20].

In some of the Russian experiments [21], the biological resonance has been found as narrow as $2 \cdot 10^8$ Hz. This can be understood on the assumption that the only broadening of the excited giant-dipole vibration arises from its electric coupling to the thin layers of structured water whose dielectric absorption lies in this region [22, 23]. The remarkable absence of other frictional effects reminds one, of course, of the various suggestions of the existence of room temperature superconductive regions in biological systems. So far no definite experimental proof for their existence has been found. These narrow resonances are most likely to occur when the level which is excited by the radiation is identical with the level which is strongly populated in Bose condensation,

(*) It should be mentioned that in [18] the presentation of a quadratic Hamiltonian is misleading, though the results are correct. For, as required, the authors do use the influence of a heat bath which in terms of a Hamiltonian would require at least 4th order terms to obtain their eq. (8*a*)—as can be seen from our eq. (3.2) which is responsible for the occurrence of a chemical potential μ.

i.e. when in (3.21) this is the level K_0. Broader bands must be expected when this is not the case.

In experiments of this type, one must be prepared for unexpected non-linear effects of the imposed radiation. Thus, within the range in which the radiation is absorbed, in the first place coherent excitation of some molecules is expected. If the same type of molecules is present at greater depth, then they in turn may become excited by transfer of the excitation energy from the outside molecules. Thus the excitation may be expected to move beyond the penetration depth of the imposed radiation.

Now, in turning to the excitation of the strongly polar metastable state, one would, of course, attempt to excite this state by bringing the molecule in question into a strong electric field. It should be of interest in this context that investigations on nerve membranes have led to the conclusion that the electric field in the membrane makes it nearly impermeable to Na^+ and K^+ ions, whereas the absence of the field leads to a much higher permeability presumably through proteins dissolved in the membrane; it is suggestive to attribute these two different properties to the two states in the proteins.

More direct evidence for conformational changes of certain molecules in membranes due to changes of the electric field is available [24].

A number of other possibilities has been discussed in [4], including results found with the electret method [25] and with laser-induced stimulation of enzyme activity at very high dilution [26].

Thus, while experiments available at present seem to support the theoretical predictions, in a general way much greater refinement of the experimental methods is desirable to obtain more specific experimental results. This in turn should stimulate theoretical investigations of a more specific nature.

7. – Cancer.

The problem of cancer is one of the control of cell division. While bacterial cells under appropriate conditions keep on dividing, cells in a fully grown differentiated tissue or organ divide relatively rarely, though they divide more rapidly in growing tissues and organs. We shall assume that a controlling agency belonging to the whole organ, *i.e.* a collective property, exists and that individual cells respond to it.

The nuclei of these cells contain a DNA-protein complex, whose detailed structure is not well known, though it seems reasonable to assume that its spacial arrangement differs in different organs and depends on the type of differentiation that has taken place. Now we shall assume that these materials are capable of electric vibrations which can be excited coherently in the sense of our model (cf. sect. **3**). Thus metabolic energy would be used to excite these vibrations at a well-defined frequency (or frequencies) which would be char-

acteristic for the particular organ or tissue. Note that experiments discussed in sect. **6** confirm the existence of such vibrations in some biological materials.

This then implies that a coherent electric vibration carried collectively by the individual nuclei extends through the whole tissue (organ), and that the vibrations of each individual cell respond to it and are thus held in the appropriate phase, such that the total electric energy is a minimum. In general, this vibrating polarization field will form a complicated spacial pattern.

Now, preceding cell division, the DNA-protein complex of the nucleus of a cell must unfold and may then be expected to change some of its physical characteristics, such that it looses its resonance with the collective mode. This implies that its energy of interaction with the collective mode is increased, *i.e.* energy has to be spent to perform this change (apart from changes in the internal energy). This energy may not always be available and, as a consequence, the interaction of an individual cell with the collective mode acts as an inhibition on cell division. The strength of this inhibition depends on the magnitude of excitation of the collective mode. This excitation may well depend on the size of the tissue because of the long range of the interactions as discussed in sect. **5**. The possibility of a size-dependent inhibition on cell division thus exists.

A situation thus prevails which in some respects corresponds to order in physical systems described in terms of an order parameter as, for instance, in lasers (cf. also [27]). In our case, the collective vibration represents the order parameter. It is built up of the contributions of the relevant vibrations of the individual cells, and they in turn obey the instruction of the order parameter, namely not to divide.

Now assume that changes have taken place in a particular cell such that its frequency is altered. This cell no longer contributes to the coherent collective vibration, whose intensity will thus be slightly reduced, nor does this cell obey the instruction of the coherent mode, *i.e.* the inhibition to divide disappears. The slight reduction of intensity of the coherent mode due to the change of property of a single cell should have a minute effect on other cells. A critical intensity should exist, however, below which the control of cell division no longer is effective. It is feasible, therefore, that something like a phase transition takes place from the controlled to the uncontrolled state once a critical number of cells has been affected.

Such an approach requires that—while the controlling vibration is strong enough—a cell in the tissue will be induced to transfer into the correctly vibrating state provided it possesses such a state, for only thus can the system exhibit stability.

This may have two types of consequences:

i) Differentiation may be expected to consist in rearrangements of the DNA-protein complex, such that it obtains relevant frequencies assumed

absent before differentiation. Under the influence of the coherently excited mode(s) of the particular tissue (organ), this transition is energetically favourable and hence is stimulated [28]. The differentiated cell then gets subjected to the control.

ii) Mutations which lead to alterations in the relevant frequency(cies) are energetically less favourable than those which do not alter them and which thus still respond to the control and are, therefore, statistically less likely.

Thus, in our model, the sufficiently excited collective vibration exerts an influence on individual cells which inhibits both cell division and « unfavourable » mutations (which would not react to control) and, at the same time, tends to bring cells which do not respond to the control into states in which they do react to it.

If by external influences some cells are changed such that their relevant frequencies are altered, then *a*) these cells no longer respond to the control and *b*) the strength of the controlling vibration is reduced. Both these effects are rectified by the above-mentioned stabilizing influence provided they are not too large. If, however, the number of altered cells is so large that the excitation of the collective mode is reduced below a critical value, then the control becomes ineffective. As a consequence, all cells divide more frequently, and simultaneously « unfavourable » mutations (having « wrong » frequencies) become possible, *i.e.* a phase transition from order to disorder (cancer) has taken place.

It should be noted here that the frequencies of the changed cells will differ from each other; thus no collective mode with sharp frequency will arise: the ordered state has a sharp frequency, the disordered one a broad frequency band.

Which are the external influences that can lead to a change in frequencies? It has been shown [2] that supply of unattached electrons could have such an influence. Such electrons might occur in the conduction band of various molecules. They are then capable of long-wave electric vibrations, plasma waves, whose frequencies increase proportional to the square root of the electron density. These vibrations will interact with the coherent vibrations of our system and under appropriate circumstances can significantly alter the frequency.

Such electrons might be supplied by excitation through ultraviolet light. Or they might be supplied by foreign molecules which are electron donors. A change of frequency might, of course, also arise from an invasion by foreign molecules into the relevant DNA-protein complex.

Other possibilities may arise, however, if we assume that the frequency sharpness found in some of the experiments discussed in sect. **6** is a feature of the proposed collective vibrations. It has been previously indicated that electric coupling with structured water would account for the measured frequency width indicating absence of all other types of friction. Some structural

changes might be sufficient to eliminate this property and with it the effectiveness of control. The affected cells could then still have frequencies in the region of the nonaffected one, but exhibit greater width.

The model described here can without difficulty be presented in mathematical form by using well-known techniques developed, *e.g.*, in connection with laser physics [29]. Even without doing so, it will be noticed that the term « collective mode » might be given a different physical interpretation from the one suggested here, provided individual cells have selective properties which enable them to react to the collective mode and which could be destroyed by external influences.

If the interpretation of the collective mode as a vibration is correct, then one would wish to know the order of magnitude of relevant frequencies. The 10^{11} Hz region is, of course, a first candidate both for theoretical and experimental reasons (sect. **3** and sect. **6**). It might well be, however, that quite different frequency regions are also of importance, and it will in the first place be a task for experiments to find these frequencies.

Most desirable would, of course, be experiments which measure the excitations of the biological material *in vivo*. For frequencies near or above 10^{12} Hz laser Raman effect would be suitable. For frequencies near or below 10^{11} Hz, this becomes inefficient because of the broadening of the primary line through water. Thus the frequencies for which selective biological effects have been discovered (sect. **6**) are beyond the available range. New methods (corresponding to Brillouin scattering) are being developed, but must still be adapted for use in biological materials.

It should be emphasized in this context that vibrations in this frequency range may very sensitively depend on details of the arrangements and on the conformation of relevant molecules including structured water and ions, which must both be considered an integral part of the system. Investigations on molecules, *e.g.* proteins, outside their natural surroundings may but need not give relevant results. Something similar holds of the measurement of absorption of electromagnetic waves by the biological material. We have mentioned above that the excited collective mode might have a complicated spacial pattern. This will probably not be optically active. Optically active modes are, however, to be expected in the neighbourhood of each « relevant » frequency; they would show up as a band rather than as the relatively sharp line we expect from the collective mode, except in cases in which the spacial pattern is homogeneous in the range of penetration of the electromagnetic wave—as might hold for thin layers of the material. It should be emphasized in this context that some of the experiments mentioned in sect. **6** exhibit extremely sharp frequency response for biological effects, whereas broad bands are found in optical measurements. Nevertheless changes found in the optical spectra would certainly indicate major changes and could thus provide valuable information.

One might in particular wish to measure the changes arising from the excitation of electrons into the conduction bands discussed above. It must be pointed out in this context that plasma waves are not optically active except through the influence of surfaces. The same is likely to hold of the collective mode with which they interact. For optical detection, therefore, one would use biological samples which are small compared with the wavelength of the electromagnetic radiation with the relevant frequency. When using a thin layer, then the electric vector should have a component perpendicular to the surface. Internal surfaces may, however, also be effective which to some extent may relax these conditions.

Finally biological effects of the electromagnetic radiation are most likely to provide significant results. If we can learn from the experiments mentioned in sect. **6**, then we might expect sharp frequency resonances in the biological response. As a consequence, a tunable source will be required.

In the first place, we would expect the naturally excited mode to be in its most favourable state. External excitation of modes with the same frequency, though probably with different spacial pattern, would thus interfere with the efficiency of the collective controlling mode. In a grown material this would then increase the rate of cell division, while in a growing system it should decrease it.

Finally, when under the influence of external agencies a sufficient number of cells have undergone changes in frequency to the extent that the controlling collective mode has become ineffective, then a stronger externally imposed vibration of the correct frequency (though possibly with different spacial pattern) might still be able to restore the original order. This, of course, would be the most startling influence of electromagnetic waves on biological systems.

Note added in proofs on 27/9/1977.

Conclusive evidence for the metabolic excitation of vibrational states in bacteria has now been obtained by Raman effect. WEBB and STONEHAM (*Phys. Lett.*, **60** A, 267 (1977)) show that, while resting bacteria exhibit only bands in the (100÷200) cm^{-1} region, active bacteria show strong lines. Moreover (S. J. WEBB, M. E. STONEHAM and H. FRÖHLICH: *Phys. Lett.*, A, in print), the intensity ratio of anti-Stokes to Stokes lines in thermal equilibrium should be about 0.5, whereas it is found close to 1.0, evidence for strong nonthermal excitation.

REFERENCES

[1] H. FRÖHLICH: in *Theoretical Physics and Biology*, edited by M. MAROIS (Amsterdam, 1969), p. 13.
[2] H. FRÖHLICH: *Int. Journ. Quart. Chem.*, **2**, 641 (1968).
[3] H. FRÖHLICH: *Riv. Nuovo Cimento*, **3**, 490 (1973).

[4] H. FRÖHLICH: *Proc. Nat. Acad. Sci.*, **72**, 4211 (1975).
[5] H. FRÖHLICH: in *Synergetics*, edited by H. HAKEN (Stuttgart, 1973), p. 241.
[6] H. FRÖHLICH: *Journ. Collective Phen.*, **1**, 101 (1973).
[7] H. FRÖHLICH: *Phys. Lett.*, **39** A, 153 (1972).
[8] H. FRÖHLICH: *Nature*, **228**, 1093 (1970).
[9] D. E. GREEN: *Ann. N.Y. Acad. Sci.*, **227**, 6 (1974).
[10] B. HOLLAND: *Journ. Theor. Biol.*, **35**, 395 (1972).
[11] J. D. WATSON: *Molecular Biology of the Gene* (New York, N. Y., 1970), p. 187.
[12] H. FRÖHLICH: in *From Theoretical Physics to Biology*, edited by M. MAROIS (Basel, 1973), p. 2.
[13] *Interaction of Weak Electric and Magnetic Fields with the Brain*, edited by W. R. ADEY and S. M. BAWIN (contribution FRÖHLICH), *Neurosci. Res. Prog. Bull.*, in print (1976).
[14] F. KAISER: *Phys. Lett.*, **62** A, 63 (1977).
[15] P. ELUL: *Relation of Neuronal Waves to E.E.G.*, *Neurosci. Res. Prog. Bull.*, **12**, 97 (1974).
[16] N. D. DEVYATKOV: *Sov. Phys. Usp.*, **16**, 568 (1974).
[17] H. FRÖHLICH: *Phys. Lett.*, **51** A, 21 (1975).
[18] D. BHAUMIK, K. BHAUMIK and B. DUTTA ROY: *Phys. Lett.*, A, in print.
[19] S. J. WEBB and D. D. DODDS: *Nature*, **218**, 374 (1968); **227**, 1199 (1969).
[20] A. J. BERTEAUD, M. DARDALHON, N. REBEYROTTE and D. AVERBECK: *Compt. Rend.*, **281** D, 843 (1975).
[21] A. Z. SMOLYANSKAYA and R. L. VILENSKAYA: *Sov. Phys. Usp.*, **16**, 571 (1974).
[22] H. P. SCHWAN: *Ann. N.Y. Acad. Sci.*, **125**, 344 (1965).
[23] E. G. GRANT: *Journ. Mol. Biol.*, **19**, 133 (1966).
[24] K. F. WIKSTROM and H. T. SAARI: *Journ. Mol. Cell. Biochem.*, **11**, 17 (1975).
[25] S. MASCARENHAS: *Journ. Electrostatics*, **1**, 141 (1975).
[26] N. KOLLIAS and W. R. MELANDER: *Phys. Lett.*, A, in print (1976).
[27] H. HAKEN: in *Synergetics*, edited by H. HAKEN (Stuttgart, 1973), p. 9.
[28] F. FRÖHLICH: in *Cooperative Phenomena*, edited by H. HAKEN and M. WAGNER (Berlin, 1973), p. xi.
[29] H. HAKEN: *Rev. Mod. Phys.*, **47**, 67 (1975).