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The Physics of DNA: Onset of Soliton-Like Excitations, Chain Relative Disorder, and Basis for a Statistical Mechanics of the Macromolecule

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A dual approach for studying the dynamics and function of DNA is proposed. Soliton-like excitations may occur under certain conditions and, via an electromagnetic signal that can modulate the soliton energy, the transition B-DNA (resting state) → A-DNA (active state) can take place. On the other hand, the Hamiltonian describing this transition can be used to construct an entropy operator for DNA and thus assess its state of relative disorder and its relationship to DNA function. Biological and medical applications of this study are put forward, as well as predictions for experimentally testing the model.

1. INTRODUCTION

It is only recently, during the last decade, that it has become apparent that theoretical physics must play a major role in the elucidation of mechanisms underlying the functioning of biological systems. Among these, the role of DNA in the initiation and maintenance of cell activity is the one requiring the most urgent attention, for obvious reasons. Although the complexity of DNA coupled to the refinement, variety, and range of functions that it performs with such admirable accuracy may detract theoreticians from ever hoping to produce a model that might predict even the simplest of DNA feats, I intend to show that this need not be so. Indeed, the aim of this paper is to show that such a model for DNA can now be at hand and that two lines of attack of the problem can usefully complement each other to provide some of the answers toward uncovering the basic mechanisms of DNA function. Section 2 puts forward the model for the onset of soliton-like excitations in DNA and its relation to both the B-DNA (resting state) and A-DNA (active state) conformations of the macromolecule. A

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formalism is proposed via an electromagnetically induced B-DNA→ A-DNA transition for a variety of DNA responses and effects to take place. Section 3 describes the role of the entropy of the chain in the assessment of the state of relative disorder, be it local (i.e., at a particular DNA locus) or general (as in cell division). This is done using the Hamiltonian described in Section 2 to construct the partition function for such a complex system as DNA, and thus its entropy. Section 4 proposes the synthesis of these complementary lines of approach through the construction of a full statistical mechanics of DNA. The implications of such a study in the fields of biophysics, biology, and medicine are analyzed in the concluding section.

The work presented in this paper is the natural continuation of work I started 4 years ago in association with Prof. Peter Beaconsfield at the SCIP Research Unit at Bedford College, London. Although the sudden and tragic death of Prof. Beaconsfield at the end of last summer ended our collaboration, I would like to pay tribute to his memory and to his inspired and pioneering conviction of the fruitfulness of the marriage between physics and biology. To him I dedicate this article.

2. MODEL FOR SOLITON-LIKE EXCITATIONS IN DNA

DNA consists of approximately 4×10^9 units (base pairs) made up of an arrangement of only four different types (the four bases abbreviated A, C, G, T), which combine only in the base pairs A–T and C–G. Intramolecular vibrations take place in the O-P-O bond of the DNA backbone (Erfurth et al., 1972; Thomas and Hartmann, 1973) and these are coupled to chain deformations resulting from the extension and compression of the hydrogen bonding between the two bases of a base pair. In fact, this coupling appears to be an indirect one mediated, to a certain extent, by C=O groups in the base pair. Nevertheless, this nonlinear coupling depends crucially on the value of the coupling constant χ_{DNA}: we have shown that, for and above a certain threshold value of χ_{DNA}, soliton formation occurs when DNA is in its B state (Balanovski and Beasconsfield, 1983). Davydov (1979a, b) has shown that, under suitable conditions, collective excitations in the form of solitons can exist in α-helix proteins. Although of a different topological nature, the Davydov soliton is the solution of a nonlinear Schrödinger equation that describes the time evolution of the distribution of intramolecular excitations (in the C=O amide I bond of the protein) over the molecules of the chain and the displacement of the molecules about their equilibrium positions. The work of Davydov was pursued by Scott (1982).

Del Giudice et al. (1982) proposed a model for DNA activity based on both Davy solitons and on Frohlich's (1975) theory of coherent electrical

excitations. The model of Del Giudice et al. presents several drawbacks (Balanovski and Beaconsfield, 1987), the main ones being: (1) an interpretation of experimental results of Webb (1980) taken under nonphysiological conditions, (2) a need to invoke two separate mechanisms, namely Davydov solitons and Frohlich's coherent excitations, to explain B-DNA and A-DNA activity, and (3) excitation of higher frequency modes first and then transition to lower frequency ones attributed to water molecules.

Englander et al. (1980) and more recently Krumhansl and Alexander (1983) proposed two different models for soliton formation in DNA, the latter having superseded the former. The latter paper presents a semiquantitative proof of the plausibility of the existence of nonlinear excitations in DNA, but, in the words of the authors, it is the beginning of a tremendous amount of work to be done to relate it to specific DNA function.

According to the Beaconsfield-Balanovski model of DNA (Balanovski and Beaconsfield, 1983), soliton formation occurs in B-DNA and is "switched on" by internal processes within the system. This "internal switch," although very complex, is mainly due to three effects: (1) strength of the nonlinear interaction in DNA, (2) energy release due to ATP hydrolysis, and (3) the constant presence of an electromagnetic (em) "background" arising from different components of a cell. The latter contributes to the DNA "ground state" and, due to our interest in processes that involve energy differences with respect to this ground state, we only study excitations of the ground state. Thus, the soliton-like excitation arising in B-DNA is responsible for the "routine maintenance" of a cell and its continuous monitoring of normal vital functions.

The next step is to understand how the switching from the B-DNA state to the A-DNA state can occur as a result of a stimulation requiring the cell to satisfy the need for, e.g., a certain protein to be synthesized. Metabolic changes associated with the requirements of the cell must be relayed on to DNA so that (1) appropriate action of a DNA-mediated process can be initiated or promoted, or (2) and "extra-DNA" process can take place, e.g., release of a sufficient amount of a certain product already made and stored in a cell organelle (as seems to be the case of albumin). If the energy change associated with the demand of the cell is greater than 0.25 eV, the threshold value for the B-DNA → A-DNA transition, said transition is effected. The nonlinear component of the em field signalling to DNA the demand of the cell has been shown to be several orders of magnitude greater than the linear one (Balanovski and Beaconsfield, 1982). This em signal couples with the chain's apparent permanent dipole moment, and this coupling may result in soliton energy modulation via a resonant-type effect in the DNA chain. Experimental evidence for these in B-DNA and A-DNA already exists (Erfurth et al., 1972; Thomas and Hartmann, 1973;

Webb, 1980; Lindsay and Powell, 1983). In turn, this soliton energy modulation can produce strong chain deformation, leading to DNA unzipping. Long-range communication effects can be understood in terms of a coherent oscillation of the segments involved (Balanovski and Beaconsfield, 1987). Presumably a particular DNA response will originate specifically from a particular em signal, mainly characterized by its frequency and power level (Balanovski and Beaconsfield, 1982). Therefore, instead of looking for the exact base sequencing associated to the initiation of a particular DNA function, we look for the characteristics of an electrical signal that could artificially reproduce the effect of, e.g., the initiation of a certain DNA function.

We now describe the formalism for DNA activity based on the above model. The Hamiltonian for the B-DNA state (routine maintenance state) can be written as (Balanovski and Beaconsfield, 1983)

$$\mathscr{H}_{\text{B-DNA}} = \mathscr{H}_0 + \mathscr{H}_1 + \mathscr{H}_2 \tag{1}$$

where

$$\mathscr{H}_0 = \frac{1}{2}\sum_n \left[\frac{1}{M}\hat{p}_n^2 + w(u_n - u_{n-1})^2\right] \tag{2}$$

is the energy operator for displacements u_n of molecules of mass M from their equilibrium position (M is here the mass of a base pair). $\hat{p}_n$ is the momentum operator canonically conjugated to u_n and w is the chain elasticity coefficient. Here

$$\mathscr{H}_1 = \sum_n [\varepsilon_0 B_n^+ B_n - J(B_{n+1}^+ B_n + B_{n+1} B_n^+)] \tag{3}$$

is the energy operator for the intramolecular excitation, where the fundamental energy of the intramolecular vibration is $\varepsilon_0 = \varepsilon - D$, with ε the excitation energy for a molecule and D the deformation energy excitation operator. The quantity $-J$ is the nearest neighbor dipole-dipole interaction energy, and B_n^+ and B_n are creation and annihilation operators for intramolecular excitation quanta on the nth molecule. The term

$$\mathscr{H}_2 = \chi_{\text{DNA}} \sum_n (u_n - u_{n-1}) B_n^+ B_n \tag{4}$$

describes the nonlinear interaction between intramolecular excitations and their displacements from equilibrium positions. We have estimated (Balanovski and Beaconsfield, 1982) the strength of the nonlinear coupling in DNA to be $\chi_{\text{DNA}} = 1.26 \times 10^{-9}$ N, which is approximately 30 times greater than the threshold for the onset of soliton formation in α-helix proteins (Scott, 1982).

The energy transfer effected by the soliton when DNA is in its B state is the solution equation (1), namely

$$E_{\text{soliton in B-DNA}} = E_{\text{exciton}} - \chi^4_{\text{DNA}}/3w^2J + \tfrac{1}{2}m_{\text{sol}}v^2_{\text{sol}} \tag{5}$$

where $E_{\text{excition}} = \varepsilon - D - 2J$, m_{sol} is the soliton mass, and v_{sol} is the soliton velocity of propagation. We have calculated the soliton mass to be (Balanovski and Beaconsfield, 1983)

$$m_{\text{soliton}} = \frac{\hbar}{2Ja^2} + \frac{4\chi^4_{\text{DNA}}(1+\frac{3}{2}s^2-\frac{1}{2}s^4)}{3w^2(1-s^2)^3Jv^2_{\text{sound}}} \tag{6}$$

where $m_{\text{exciton}} = \hbar/2Ja^2$ and $s = v_{\text{soliton}}/v_{\text{sound}}$, with a being the distance between two neighboring base pairs along the DNA chain and v_{sound} the velocity of longitudinal sound along the DNA chain.

The Hamiltonian describing the transition into the A-DNA state (active state) is

$$\mathcal{H}_{\text{A-DNA}} = \mathcal{H}_{\text{B-DNA}} + \mathcal{H}_{\text{int}} \tag{7}$$

where $\mathcal{H}_{\text{int}}$, an operator that will allow for soliton energy modulation induced by the external em signal, will be responsible for the initiation of DNA function. Physically, it describes the energetic changes occurring to B-DNA in the presence of this external em signal, which, if above the threshold value, can induce induce the transition into the A-state. $\mathcal{H}_{\text{int}}$ is mainly the interaction between the em field and the longitudinal dipole–dipole coupling of the chain. The energy transfer along the chain in the A state is the solution to equation (7), namely

$$E_{\text{soliton in A-DNA}} = \varepsilon - D - 2J - \chi^4/3w^2J + \tfrac{1}{2}m^*_{\text{sol}}v^2 \tag{8}$$

The last term in equation (8) describes the A-DNA chain energy, where v is the new soliton velocity in the A-DNA conformation and m^* is the new effective soliton mass accounting for the coupling between the external em field and J. We have already recognized the importance of nonlinear electric field effects on DNA (Balanovski and Beaconsfield, 1982). The nonlinear component of the interaction energy will produce the soliton energy modulation required to produce chain deformation and induce the B-DNA→ A-DNA transition. We have given an example of a calculation of this nonlinear effect in the case of a signal simulating conditions for a DNA-mediated insulin synthesis triggered by an increase in glucose level (Balanovski and Beaconsfield, 1984a, 1987). Indeed, we predicted the main parameters describing the signal that would artificially reproduce the effect. These predictions are now being tested in the laboratory of the Dielectrics Group at the Physics Department, King's College.

3. THE COMPLEMENTARY APPROACH: ROLE OF NEGATIVE ENTROPY IN ASSESSING THE STATE OF RELATIVE DISORDER OF THE DNA CHAIN

We now present how, using the Hamiltonian described by equation (1), namely $\mathcal{H}_{\text{B-DNA}}$, or that described by equation (7), $\mathcal{H}_{\text{A-DNA}}$, it is possible to assess the state of relative disorder of the DNA chain in either of its two conformations B-DNA and A-DNA.

We have already presented the idea of the complementarity of order and disorder in biophysical systems, in particular its correlation between structure and function of DNA (Balanovski and Beaconsfield, 1984b). In that paper, negative entropy S is introduced as a measure of the order of the DNA chain, and temperature T as a measure of its disorder. If we consider the dynamical situation of groups of bases that have to be opened or closed when, e.g., a certain protein has to be produced, we can correlate that particular DNA "configuration" with that particular function to be performed. Opening of the relevant base pairs must be an energetically favourable situation and must correspond to the probability for maximum disorder existing in that particular configuration. This clearly shows that the variable asessing the state of relative disorder of the DNA chain must also be a function of the energy of the system.

We can thus consider constructing the statistical mechanics of the "soliton gas" described by $\mathcal{H}_{\text{B-DNA}}$ and define the partition function

$$Z_{\text{B}} = \sum_{\{\mathcal{H}_{\text{B-DNA}}\}} e^{-\beta \mathcal{H}_{\text{B-DNA}}}$$

where $\{\mathcal{H}_{\text{B-DNA}}\}$ indicates the set of all possible values of $\mathcal{H}_{\text{B-DNA}}$, $\beta = 1/kT$, k is the Boltzmann constant, and T is the absolute temperature. The soliton free energy F can be calculated as

$$F = -\frac{1}{\beta} \ln Z_{\text{B}} = E_{\text{sol}} + TS \tag{9}$$

where E_{sol} is the soliton internal energy and S the negative entropy, the measure of the order of the system.

But

$$S_{\text{B}} = \frac{\partial F}{\partial T} = \frac{\partial}{\partial T}(-kT \ln Z_{\text{B}})$$

since E_{sol} is not explicitly dependent on temperature. Thus

$$S_{\text{B}} = -\left(k \ln Z_{\text{B}} + kT \frac{\partial(\ln Z_{\text{B}})}{\partial T}\right) \tag{10}$$

or even

$$S_B = -k\left(\ln Z_B + T\frac{1}{Z_B}\frac{\partial Z_B}{\partial T}\right) \tag{11}$$

Since $\mathcal{H}_{\text{B-DNA}} = \mathcal{H}_0 + \mathcal{H}_1 + \mathcal{H}_2$, the partition function can be separated into

$$Z_B = \sum_{\{\mathcal{H}_{\text{B-DNA}}\}} e^{-\beta\mathcal{H}_0} e^{-\beta\mathcal{H}_1} e^{-\beta\mathcal{H}_2} \tag{12}$$

We can transform the three terms of equation (1), namely $\mathcal{H}_{\text{B-DNA}}$, into the continuum representation in the following way. In

$$\mathcal{H}_0 = \tfrac{1}{2}\sum_n \left[\frac{1}{M}\hat{p}_n^2 + w(u_n - u_{n-1})^2\right]$$

we define

$$\rho_n \equiv u_n - u_{n-1}, \qquad M\,\partial\rho_l/\partial t \equiv \hat{p}_l \tag{13}$$

Therefore we get

$$\mathcal{H}_0 = \sum_n \left\{\frac{M}{2}\left[\sum_{l=n}^{\infty}\frac{\partial\rho_l}{\partial t}\right]^2 + w\rho_n^2\right\} \tag{14}$$

But also

$$\rho_n = (pD/2wa)\,|\alpha_n(t)|^2 \tag{15}$$

where $\alpha_n(t)$ characterizes the distribution of intramolecular excitations over the molecules of the chain. Thus we are left with

$$\mathcal{H}_0 = \tfrac{1}{2}\sum_n \left\{F\left[\sum_{l=n}\frac{\partial}{\partial t}|\alpha_l(t)|^2\right]^2 + G\,|\alpha_n(t)|^4\right\} \tag{16}$$

where $F = MG/2w$ and $G = p^2D^2/2wa^2$. In terms of the field parameter $\varphi(\xi, t)$, with ξ being the dimensionless coordinate, equation (1) then becomes

$$\mathcal{H}_{\text{B-DNA}} = \frac{J\partial^2}{\partial\xi^2} - \left[\varepsilon - 2J - D + \frac{1}{2}\int_{-\infty}^{\infty} d\xi\left\{\int_{\xi}^{\infty} F\left[d\eta\frac{\partial}{\partial t}|\varphi(\xi, t)| + G\,|\varphi(\xi, t|^2\right]^2 + G\,|\varphi|^2\right\}\right] \tag{17}$$

Calculation of the partition function Z_B is thus the calculation of the functional integral

$$Z_B = \int \mathcal{D}(\dot{\phi}, \phi)\exp\left[-\beta\int dx\,\mathcal{H}(\dot{\phi}, \phi_x, \phi)\right] \tag{18}$$

The details of this calculation will appear in a future communication. Suffice it for now to put forward the usefulness of the calculation of this expression for the partition function Z_B.

According to equation (11), we can calculate the negative entropy $S_{B\text{-}DNA}$, giving us an estimate of the state of relative disorder in B-DNA and therefore setting a "basal state." At the time when a particular DNA response is initiated or triggered, a specific em stimulation induces the B-DNA→A-DNA transition. This is described in Balanovski and Beaconsfield (1984a, 1987). This transition is in turn described by equation (7) for $\mathcal{H}_{A\text{-}DNA}$, in which $\mathcal{H}_{int}$ contains the specific information needed for DNA to initiate the transition and unzip the corresponding segments of DNA relating to that particular demand. Again, both Z_A and Z_{int} can be put into the continuum representation as indicated by the method leading to equation (18).

The energy change described by equation (7), brought about by the above-mentioned em stimulation, would produce a change in the partition function. Namely,

$$Z_A = \sum_{\{\mathcal{H}_{A\text{-}DNA}\}} e^{-\beta \mathcal{H}_{A\text{-}DNA}} \tag{19}$$

where $\{\mathcal{H}_{A\text{-}DNA}\}$ indicates the set of all possible values of $\mathcal{H}_{A\text{-}DNA}$. Bearing in mind equation (7), this is

$$Z_A = Z_B \cdot Z_{int} \tag{20}$$

This in turn will produce a change in the negentropy S_A,

$$S_A = \frac{\partial}{\partial T}(-kT \ln Z_A) \tag{21}$$

or

$$S_A = S_B + S_{int} \tag{22}$$

if we call

$$S_{int} = \frac{\partial}{\partial T}(-kT \ln Z_{int}), \qquad Z_{int} = \sum_{\{\mathcal{H}_{A\text{-}DNA}\}} e^{-\beta \mathcal{H}_{int}}$$

It can be seen that a new state of relative disorder of the DNA macromolecule can be inferred from the previous equation, and that it depends crucially on the magnitude of $\mathcal{H}_{int}$, which in turn will reflect the extent of the soliton energy modulation effected by the em signal that induced the transition

into the A-DNA conformation. Two extreme examples can be considered, one corresponding to the maximum and one to the minimum relative disorder. Setting $\partial S/\partial E = 0$ gives us the necessary condition for either maximum or minimum relative disorder. If $\partial^2 S/\partial E^2 < 0$, this implies maximum relative disorder in the DNA macromolecule, such as that in the case of cell replication where DNA unzips completely; on the other hand, $\partial^2 S/\partial E^2 > 0$ implies minimum relative disorder, as in the case of initiation of protein production where DNA unzipping is local, or the case of cell repair.

4. THE PHYSICS OF DNA AND THE BIOLOGICAL CONNECTION

In this section, I would like to relate the physical model described in this paper to biological facts (known and unknown), draw some conclusions from biological experiments (mainly on torsion, water-binding to DNA, and protein binding), and point out the lack of convincing mechanisms underlying DNA function in general.

DNA is known to function as the source of genetic information by interacting with proteins (from polymerases to enzymes) that copy it into a strand of a similar nucleic acid, RNA. The question is: which genes are to be transcribed into RNA for subsequent translation into protein, and when? From the molecular biology viewpoint, this control is exerted at the level of RNA-polymerase binding. Polymerase binding starts at the beginning of the gene to be copied: at the *promoter* site. But the question still remains: how is the binding strength regulated? How does polymerase distinguish specific gene sequences? Again, molecular biology tells us that the specificity of recognition arises from the formation of specific hydrogen bonds (link between amino acid chain in a protein and acceptor/donor in nucleotide bases). Now, how does the variability of DNA's conformation enter into interactions of this kind? DNA seems to deform somewhat to accommodate a protein, as has been shown in experiments of drug intercalation into DNA (Sobell et al., 1977), which prove DNA's flexibility.

In B-DNA, the helical twist angle between base pairs and the tilt of the bases depend on which nucleotides are adjacent to each other in the sequence. These small variations in the helix can cause atoms (even DNA phosphates) to be displaced about their equilibrium positions by 0.1 nm. This cooperative effect and its nonlinear coupling to the nearest neighbor dipole-dipole interaction along the DNA backbone is, partly, the "internal switch" for solitons in DNA. The questions of how to turn on only the genes relevant to a particular function, or as to how action at a distance occurs in DNA, have only been partly accounted for. The suggestion is that

a certain amount of DNA modulation must occur, and that protein binding is responsible for it and indeed is the main regulatory process in DNA.

This leads us to consider the importance of the multiplicity of protein function, in the case of their being structural components as well as messengers, receptors of messengers, individual identity markers, and weapons that attack cells bearing foreign markers. Some proteins bind to DNA by maximizing hydrogen-bonding interactions with a particular base-pair sequence. Others take part in replication, transcription, and translation of genetic information. Other proteins, enzymes, are crucially important catalysts involved in much of DNA function. Although it is clear that proteins work by selectively binding to molecules, we do not know how they recognize the molecules to which they have to bind and also what they recognize. In a structural protein, binding links identical molecules. Other proteins have an affinity for a molecule different from themselves: antibodies bind to specific antigens, hemoglobin to oxygen, regulators of genetic expression bind to specific patterns of DNA bases, receptor proteins embedded in the cell membrane recognize messenger molecules (hormones, neurotransmitters), which may be proteins with a specific affinity for the receptors. However, the question still is: how is the recognition achieved? Through what particular mechanism?

A similar situation occurs with enzymes that do not intervene chemically in a particular reaction, but speed the reaction by lowering an energy barrier. What mechanism is operating that allows for enzyme release and for it to recognize the substrate molecule to which it has to bind?

If we now look at the immune system and its functioning, the crucial event is the recognition of markers that distinguish self from foreign molecules. There are three different methods of action. First, we have recognition proteins, antibodies that cannot destroy a foreign organism directly, but mark it for destruction by other defensive systems. But how does an antibody molecule recognize an antigen? From the molecular biology viewpoint, it is said that it recognizes the sequence of amino acids in the hypervariable regions in the terminal regions of the arms of the Y. But what is it that they recognize in this sequence of amino acids that tells them which specific antigen it is? Second, T-cell receptors recognize only cells that bear self and foreign markers. Among T cells, there are three different classes: (1) Cytotoxic T-cells kill their targets directly. However, it is not known how they recognize target cells. (2) T-helper cells stimulate other components of the immune system when they recognize a particular antigen through an unknown mechanism. (3) T-suppressor cells diminish the activity of other components of the immune system when they recognize a particular antigen through an as yet unknown mechanism. Third, B cells manufacture antibodies that recognize a specific antigen. Here, how the B

cells recognize the antigen to know (1) that antibody has to be manufactured and (2) which antibody must be manufactured are unknown.

In the case of protein production and action of the immune system (Balanovski, 1987a), the model previously proposed suggests that the presence of an antigen or the change leading to protein synthesis are recognized as an energetic change by DNA. It is the em signal corresponding to this change that is being recognized by DNA, which in turn leads to the release of a variety of enzymes to accelerate the reaction after it has been initiated.

Similar questions arise in the processes of cell repair and cell replication. How can a missing or a changed DNA base be recognized so as to trigger initiation of repair pathways, which are then catalyzed and controlled by enzymes such as DNA polymerase and ligase? According to our model (Balanovski, 1987b), what is being recognized is a lowering of the energy of the DNA chain produced by the depurination or deamination (small energetic changes), or the larger energetic distortion produced by a "bulky lesion." This energy change then switches on the chain of events starting with the release of the enzyme that recognizes the lesion and ending with the DNA ligase sealing the repair.

In the case of cell replication, other questions arise. Replication involves polymerization rates of the order of 50 per second in mammals. Although it is known that this is mainly achieved by the action of a multienzyme complex, however many enzymes are present, they cannot initiate the process itself, but only accelerate and control it. So here again, the details of the initiation mechanisms of the process are unknown.

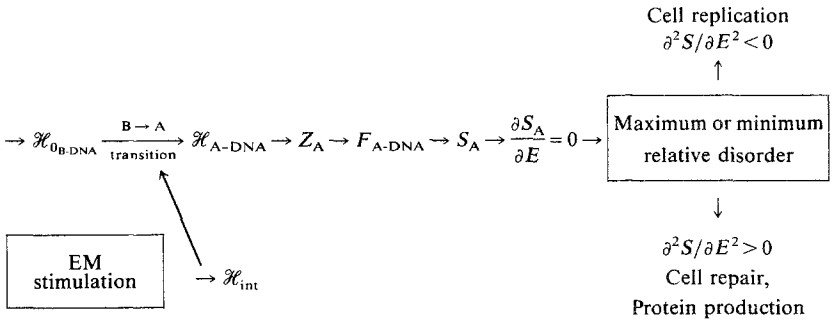
From the viewpoint of our model (Balanovski, 1987b), the dipole moment of a cluster of 50 replication origins interacting with the saturation value of the DNA electric field gives an energetic change greater than the threshold value for B-DNA to A-DNA transition. Within the context of the replication process, this transition can be thought of as a possible precursor step of single-stranded DNA, necessary for base pairing ultimately leading to the new daughter DNA. This initiation mechanism is then catalyzed and controlled by enzymes, some of which are the same as those for cell repair.

I would like to end this section with some comments about water binding. A model has been proposed (Clegg, 1981) to account for some of the special properties of water not bound to macromolecules but in their vicinity: (1) lowering of the dielectric constant (Masuzawa and Sterling, 1968), (2) inability to dissolve electrolytes (Cooke and Kuntz, 1974). According to NMR and neutron scattering experiments (Kuntz, 1971; Rydzy, 1980; Dahlborg et al., 1980), this type of water could exhibit a coherence among water dipoles induced by its long-range interaction with the macromolecules of the system. Water molecules also exhibit a broad Raman spectrum, which falls in the same range as others mentioned elsewhere (Balanovski and

Beaconsfield, 1985). It is possible that water present in DNA solutions near the macromolecule has greater mobility along the DNA axis than in the transverse direction (Dahlborg et al., 1980).

5. A SEARCH FOR A NEW METHODOLOGY FOR DECODING DNA FUNCTION

The following scheme summarizes the methodology proposed in Sections 2 and 3:



The two complementary lines of approach involve the dynamical analysis of DNA by means of $\mathcal{H}_{B\text{-}DNA}$ (when in its B state) and of $\mathcal{H}_{A\text{-}DNA} = \mathcal{H}_{B\text{-}DNA} + \mathcal{H}_{int}$ when in its A state, and the assessment of the state of relative disorder correlated with a specific function to be performed by DNA by means of the entropy operator S_A and the analysis of its maxima or minima. Bearing in mind that it has taken 30 years to decode 10% of the DNA of *Eschirichia coli*, which is approximately 1% of the size of human DNA, a rough estimate predicts complete decoding of human DNA in about 10,000 years, even allowing for major advances in computer technology. There is clearly an urgent need to complement the present base-sequencing technique with another tool that will allow us to gain information or DNA function.

The methodology presented above makes it possible to simulate some DNA functions without any need to know the exact base sequencing, since once we recognize which em stimulation produces/initiates which DNA effect, it can reproduced at will. Tests are now being conducted to assess experimentally the potentialities of this new methodology and will be reported upon shortly. If proved correct, the biophysical, biological, and medical implications are tremendous. In particular, it could be a valuable tool in the study of cell degenerative processes, such as abnormal replication leading to carcinogenic processes, the study of mutations, a possible treatment for certain types of diabetes characterized by insufficient insulin

synthesis by the pancreas, acceleration of cell repair mechanisms, and cell growth.

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