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Cross Correlation Functions in Protein Dynamics and Function.

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Dedicated to Prof. Giorgio Careri

Abstract

The role of time cross correlation functions induced in liquid water by protein function and dynamics is discussed in the context of recent computer simulations of the gramicidin channel by Swamy and Clementi. On the basis of time autocorrelation functions altready computed for this system, such as the orientational and linear velocity auto-correlation functions of the water molecules arranged around the gramicidin channel, it is concluded that cross correlation functions can play a determining role in protein function by controlling the aqueous solvation dynamics at a fundamental, single molecule level. In the manner of Careri, to whom this article is dedicated, this shows how details of molecular dynamics at fundamental level can be used to synthesise macroscopic protein function by using the global approach to computer simulation.

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Introduction

In a recent article at the International Symposium on the Structure and Dynamics of Nucleic Acids and Proteins[1] Careri suggested that when dealing with the complex dynamics and function of proteins it should be considered how "a macroscopic description level of biological significance can be related to the knowledge of microscopic physical details". In this article, we illustrate this statement with regard to the solvated dynamics of protein segments as computer simulated[2-4] with interaction potentials derived ab initio. Particular emphasis is put,following Careri[1], on the role of time dependent statistical cross correlation functions, which control the individual molecular, ionic and residue dynamics at a fundamental level, and therefore lead directly to an explanation of how a protein functions at intermediate and macroscopic levels of description. In the spirit of Careri's work[1], this is a direct application of the fundamental laws of physics to realistic biomolecular systems: 1) ion transport through Gramicidin A (GA) transmembrane channel, and 2) the hydration structure and dynamics of B and Z DNA in the presence of counterions.

The present article is based on previous work[2,3] by Swamy and Clementi who have carried out a state of the art computer simulation of these systems on the ICAP 1 and 2 systems at the Laboratory for Scientific Engineering Computations at I.B.M. Kingston, New York. In the DNA simulation, for example, both B and Z DNA were investigated in a solvated environment that contained water molecules and counter ions. The nucleic acids were held rigid, one turn of the B-DNA helix was considered in the presence of 1500 water molecules and 20 K counter ions. One turn of Z DNA was considered in thepresence of 1851 water molecules and 24 K counterions.In both the DNA and gramicidin systems the structural and dynamical properties of the water molecules solvating the counterions and the phosphate groups were investigated in some detail. Diffusion coefficients and linear centre of mass velocity autocorrelation functions were computed both for the ions and the water molecules. The velocity autocorrelation functions for the ions showed libration in a cage, and the dipole (orientational) autocorrelation functions for the water molecules indicated that those close to the helix retain memory of their initial orientations for longer intervals of time than those away from the helix. The probability distribution functions for the ions showed a well defined pattern suggesting limited mobility close to the helix. For gramicidin the application of an electric field showed that ion transport through the channel was helped considerably by the presence of two solvating water molecules, without which the process did not occur. Video animations clearly illustrated this process.

Dynamics of B and Z DNA

The network of water molecules solvating DNA has been simulated and described in detail using Monte Carlo simulation by Clementi and Corongiu[4] and these results are reproduced in Figs (1) to (4) reproduced from their paper. The water molecules are arranged in solvation cells around the DNA helix. In the first solvation cell we have water molecules bound to hydrophilic sites and near hydrophobic sites, the latter acting as bridges between the former. Thus, the first solvation shell contains a bound distribution of water molecules, the difference between the total and first solvation cell distributions defines the major and minor grooves as investigated using Monte Carlo methods by Clementi and Corongiu[4].

The dynamical properties of these systems were first investigated by Swamy and Clementi[2,3] by dividing the computer simulation into several cylindrical sub-shells of radius 3.0 A with origin at the centre of the helix.

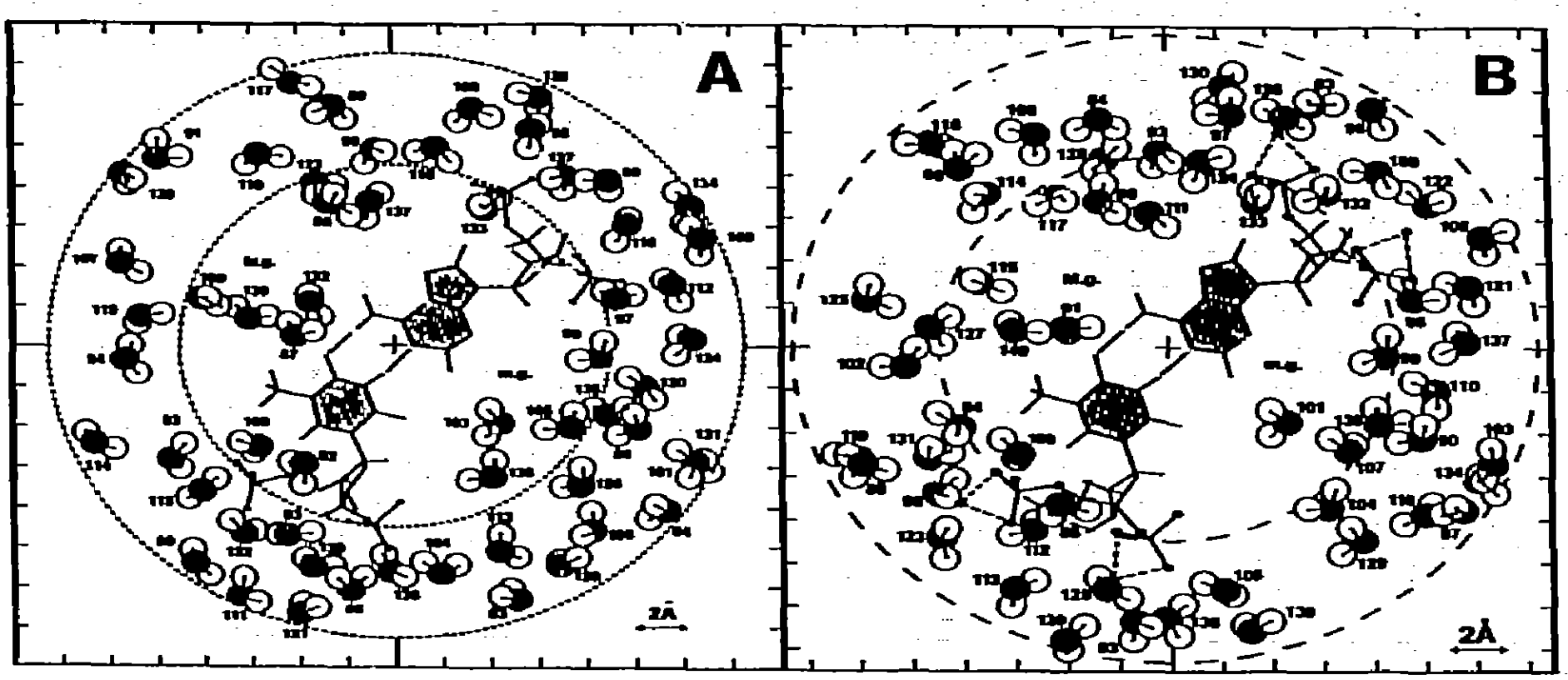

Fig. 1: Water molecules contained in a disk of 4 A thickness and solvating B-DNA (A) and Na B-DNA (B). Reproduced fromreference (4) of this paper.

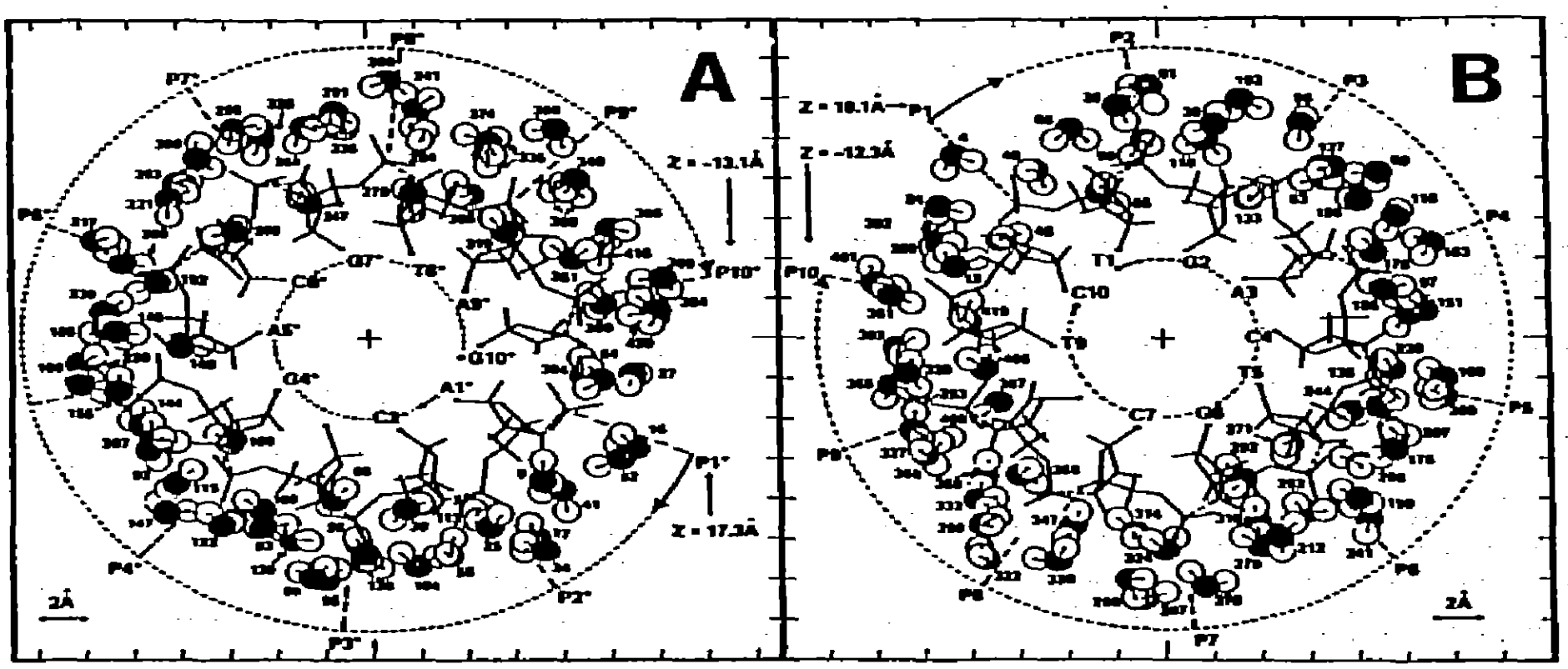

Fig. 2: Water molecules solvating the h helix and h* helix in B-DNA, (A and B respectively). Reproduced from reference (4) of this paper.

The sub-shell furthest from the helix contains only water molecules. The dynamical properties were computed in each sub-shell and compared with those averaged over the entire system. These authors found that the auto-correlation function of the water molecule's dipole moment (the "orientational a.c.f.") decays more quickly in shells away from the helix, and for sub-shells five to eight the behaviour is essentially that of free water. The Debye relaxation time for B-DNA was simulated as 25.7 ps, 10.1 ps and 3.0 ps for shells 2, 3, and 8 respectively. The corresponding numbers for Z-DNA were 8.8, 6.2 and 3.0 ps respectively.

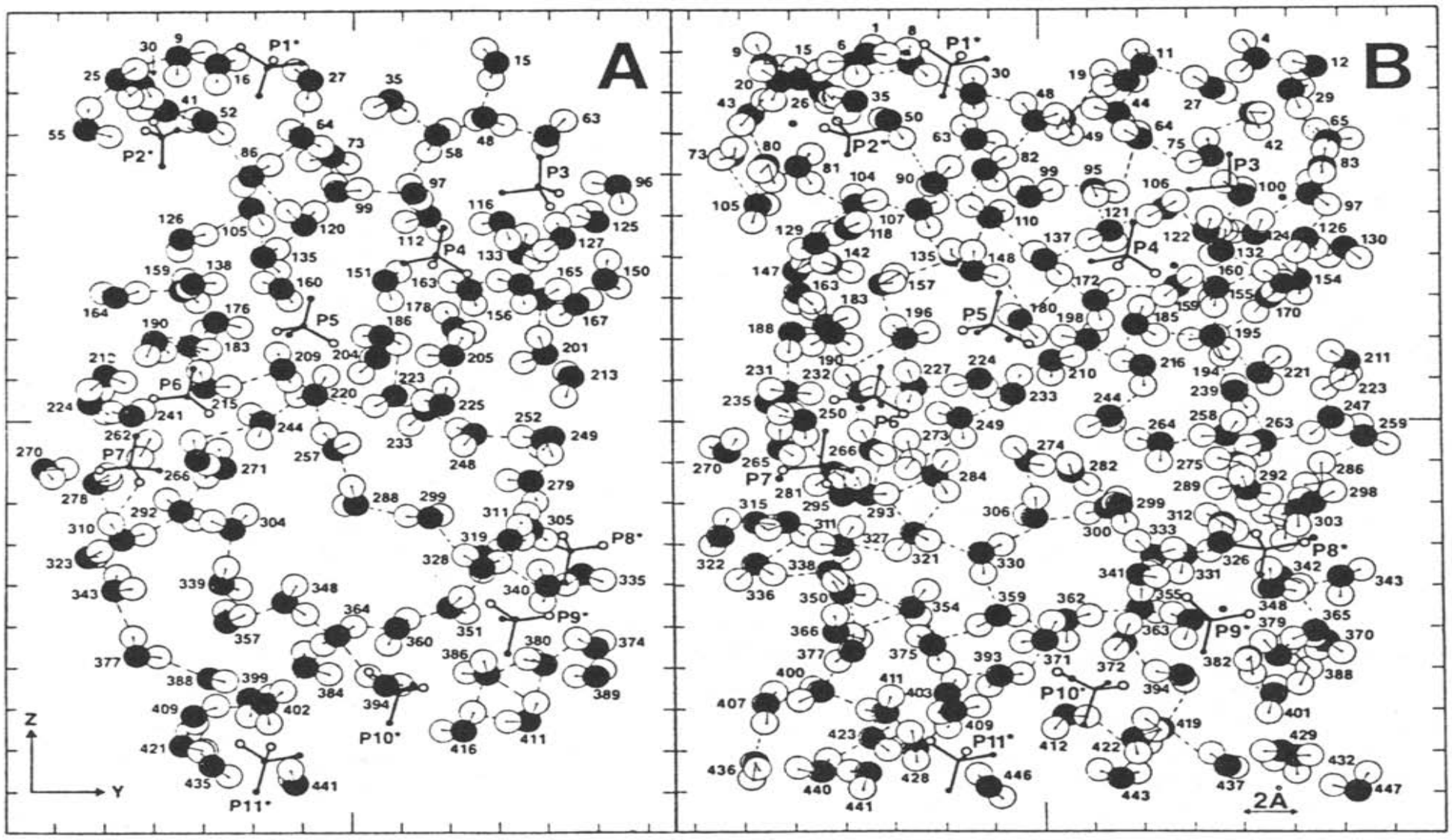

Fig. 3: Network of water molecules in B-DNA (A) and Na B-DNA. Reproduced from reference (4) of this paper.

The linear velocity autocorrelation functions for the B and Z DNA solvated systems were computed for the complete system for the counter ions. The ion linear velocity a.c.f.'s are damped oscillatory, and characteristic of rattling motion in a potential well. The complete velocity correlation function of the water molecules in the first hydration cell was also computed, as defined by

$$C_S(t) = \frac{< \sum_i v_S(t) \bullet \sum_i v_S(0) >}{< \sum_i v_S(0) \bullet \sum_i v_S(0) >} \qquad (1)$$

and where the summation extends over all the water molecules that form the first hydration shell (all those with oxygen atoms within 3.4 A of the ion, the first minimum in the oxygen-ion radial distribution functions). For the velocity a.c.f.'s close to the helix, there are high frequency oscillations which gradually disappear. In ref. (2) p. 1923 it was mentioned that time cross correlation functions would be reported, and these are predicted theoretically in the next section. The a.c.f.'s a described in references (2) and (3) show clearly many novel features of the dynamics as originally simulated[2,3] by Swamy and Clementi. For example, the helix has a tendency to pull waters around, forming spiralling density gradients. This is a chiral field influence which will be analysed in this work in terms of cross correlation effects generated by the application of the newly

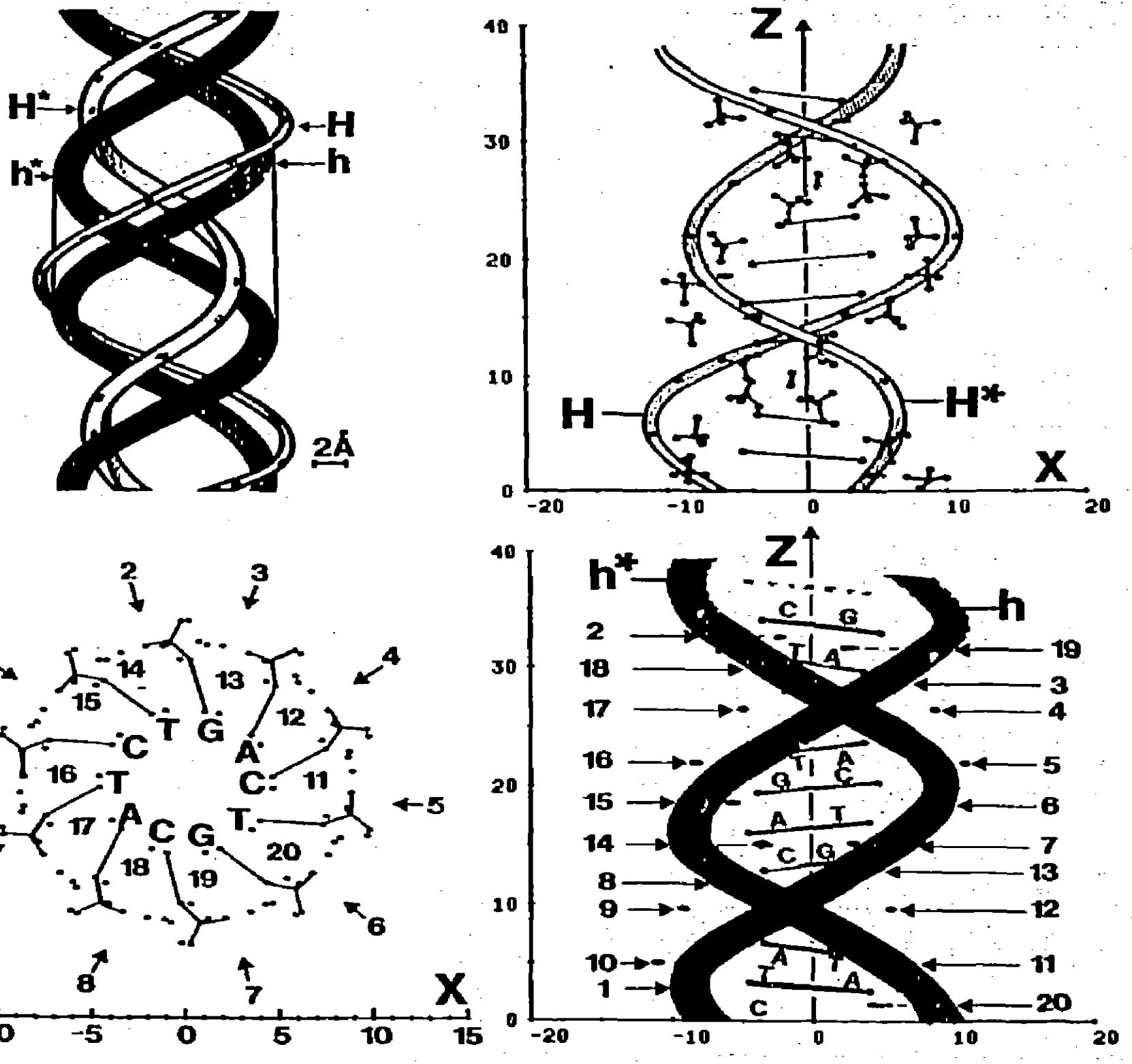

Fig. 4: Bottom left: projection of the statistical distribution of the twenty counter ions in the X-Y plane of B-DNA. Bottom right: same, X-Z plane; Top-right, as for bottom right, but with connecting helices for the ions rather than phosphate groups; Top-left, combination of top right and bottom right for more than one B-DNA turn. Reproduced from reference (4) of this paper.

developed methods[5-10] of group theoretical statistical dynamics. The ions tend to spend most of their time close to the helix, and in consequence their simulated diffusion coefficient is much smaller than in a free ionic environment. There is a well defined counterion pattern, as previously suggested by the work of Clementi and Corongiu, using Monte-Carlo simulation[4]. These arrangements, reproduced from ref. (4), are illustrated in Figs. (1) to (4) pf this paper. Further illustrations are provided by Swamy and Clementi in refs. (2) and (3), and in a video animation by Swamy available from Dept. 48B / 428, I.B.M. Kingston.

The Principles of Group Theoretical Statistical Mechanics

Before considering the newly developed principles of, and background to, group theoretical statistical mechanics, we refer to some remarks by Careri[1] which seem to presage the need for investigating statistical cross correlations. Careri refers to these in a slightly different context from the one to be pursued here, but it is worthwhile on the occasion of this Special Issue to quote his recent views as follows (ref. (1), p. 10). "Once a set of relevant macrovariables is identified, one should proceed to find their statistical cross-correlations to derive the natural laws which describe the behaviour of this macromolecule. Such is the final aim of this (local) description level, and it is obviously quite remote because of the nonlinear coupling which exists between macrovariables themselves. In the linear Onsager regime, the coupling between the time derivatives of statistical macrovariables (fluxes) and the entropy changes connected with the variation of these macrovariables (generalised forces) can be suitably expressed to let the kinetic coupling between macrovariables themselves appear in the Fourier components of their time fluctuations. Therefore this linear treatment already concerns velocities as well as space variables of the system, and it is already a considerable improvement over equilibrium thermodynamics, where only static quantities are considered."

The principles of group theoretical statistical mechanics, together with the new fluctuation-dissipation theorems of Evans and Morriss[11], are used as follows to provide support for the need to investigate statistical cross correlations between molecular dynamical variables at the fundamental level. These cross correlations are assumed to propagate to the level considered by Careri[1], and provide a way of extending the Onsager Reciprocal Principle operative at field-free equilibrium, or otherwise close to equilibrium, to the non-equilibrium statistical regime described in detail by molecular level time cross correlation functions (c.c.f.'s) mentioned in ref. (2) by Swamy and Clementi. These can be computer simulated in detail[12-20]. In the solvation shells close to a DNA helix there is a strong field influence which affects the time dependence of non-equilibrium statistical mechanical processes and equilibrium time correlation functions such as those in the work[2,3] of Swamy and Clementi.

The principles themselves are based on the application of the fundamentals of point group theory to statistical mechanics in the laboratory frame (X, Y, Z) and in the molecule fixed frame (x, y, z) of the molecular point group character tables. The relevant point group in (X, Y, Z) is the rotation-reflection group of three dimensional isotropic space, $R_h(3)$. The irreducible representations of this point group are the well- known D representations[21-23]. In this notation a scalar quantity is denoted $D_g^{(0)}$, a pseudoscalar is $D_u^{(0)}$, a polar vector such as linear velocity is $D_u^{(1)}$, an axial vector such as molecular angular velocity or orbital angular velocity, is $D_g^{(1)}$, and higher order tensors are denoted by g or u subscripts and higher order superscripts. The former denote whether a quantity is even (g) or odd (u) to parity reversal, i.e (X, Y, Z) → (-X, -Y, -Z) and the latter the order of the spherical harmonic. The symmetry signatures of time correlation functions are described using the Clebsch-Gordan Theorem to determine the D components of the product of irreducible representations of the individual dynamical components of the time correlation function. For example, the symmetry signature of the generic auto-correlation function in frame (X, Y, Z) is

$$\Gamma(A)\Gamma(A) = D_g^{(1)}D_g^{(1)}|D_u^{(1)}D_u^{(1)} = D_g^{(0)} + D_g^{(1)} + D_g^{(2)} \qquad (2)$$

depending on whether the vector A is even (g) or odd (u) to parity reversal symmetry. In eqn (2) the Clebsch-

Gordan Theorem

$$D^{(n)}D^{(m)} = D^{(n+m)} + ... + D^{(|n-m|)} \tag{3}$$

has been used to expand the product of D representations. In eqns. (2) and (3) we have assumed that the symmetry signature of the ensemble average is the same as that of the quantity being averaged, anticipating the first principle of group theoretical statistical mechanics (g.t.s.m.).

Principle 1, Neumann's Principle

The thermodynamic ensemble average <ABC....> over ABC.... exists in general if the product of symmetry representations of A, B, C,... in the point group $R_h(3)$ contains at least once the totally symmetric representation $D_g^{(0)}$.

Principle 2

This ensemble average exists in the frame (x, y, z) of the molecular point group if the product of symmetry representations of A, B, C,... in this frame contains at least once the totally symmetric representation of the molecular point group.

Principle 3

In a steady state in the presence of an applied field new ensemble averages may appear whose symmetry is that of the field.

Application to the Hydrated Protein System

The application of these three principles to the protein system considered by Clementi and co-workers may be made by considering the DNA or gramicidin helix as forming a field which affects the dynamics of the ensemble of water molecules and counter ions. The helix field will be most effective in the inner shell, and least effective in the outer shell as defined by Swamy and Clementi. Therefore, the nature of time cross correlation functions will gradually become different from inner to outer hydration shell. In the shells nearest the helical segment of DNA or gramicidin it is expected that principle (3) will be effective, and ensemble averages will be induced with the symmetry of the helix field. Assuming, for example, that this exerts a Z axis electric field of $D_g^{(1)}$ symmetry, time cross correlation functions of this symmetry will be expected in the laboratory frame in the innermost hydration cell. An example is[24] the cross correlation function between molecular linear and angular velocity

$$< v_Y(0)\omega_X(t) > = - < v_X(0)\omega_Y(t) > \tag{4}$$

which is a vector product with the same $D_g^{(1)}$ symmetry as the Z axis electric field. This type of time cross correlation function controls the aqueous dynamics in the inner shell and is induced in the laboratory frame by the assumed net Z-axis electric field generated by the helix.

The results of Swamy and Clementi strongly suggest that some kind of field is exerted by the helix because the orientational and linear diffusional dynamics of the inner shell water molecules are markedly different

from those of free water. These "bound water" dynamics are more extensively cross correlated. We have assumed in arriving at eqn. (4) via principle (3) that the influence exerted by the helix on the water molecule dynamics is a simple Z axis electric field in the first approximation. A more realistic assumption might be that the helix generates a helical field, which produces a chiral influence on the innermost shell water molecules. The symmetry of this chiral influence is as defined recently by Barron[25] i.e. odd to parity reversal symmetry and even to time reversal symmetry. The simplest type of chiral field has the symmetry signature

$$D_{chiral} = D_u^{(0)} + D_u^{(1)} + D_u^{(2)} \qquad (5)$$

and is capable of setting up scalar, vector and tensor type cross correlation functions in the innermost hydration shell of Swamy and Clementi. These cross correlation functions are ungerade to parity reversal symmetry, consisting of trace, vector (time anti symmetric) and tensor, (time symmetric) components analogous to those recently discovered in a shearing field (of gerade symmetry) by Evans and Heyes[26-28].

Utilising the molecule fixed frame of the standard point group character tables of group theory provides another means of investigating time cross correlation functions in the shells defined by Swamy and Clementi. In this molecule fixed frame it is known from the extensive computer simulations of the present author[29] that cross correlation functions exist as determined by principle (2) of group theoretical statistical mechanics, both in the presence and absence of external fields. In this frame therefore, it would be possible to investigate directly the difference in statistical cross correlations from innermost to outermost hydration shells. A large set of such cross correlation functions is available for fine-tuned investigations of this type.

We note finally that these methods can be applied to all parts of the system, for example the counterions and intra-helix dynamics as well as those of the aqueous hydration shells.

Link with New Fluctuation-Dissipation Theorems

G. P. Morriss and D. J. Evans[11] have recently derived an important new theorem which links applied forces and dissipative fluxes in atomic and molecular ensembles for arbitrary field strengths. This theorem has recently been used by M. W. Evans and D. M. Heyes[30] to extend principles (1) to (3) to non linear processes and field induced transients linked by the Morriss / D. J. Evans Theorem to induced cross correlation functions. These generalise the Green Kubo and Onsager Casimir relations and are applicable for transient dynamics in the first hydration shells of the segmental protein fragments considered by Swamy and Clementi. This offers much scope for future computer simulations, pioneered by Clementi and co-workers, and for direct applications of physics to biomolecules in the spirit of Careri.

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