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LETTER TO THE EDITOR

Statistical mechanical model for proton transfer in RNA

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Abstract. We determine the role of domain walls travelling along the backbone of an RNA double stranded helix in proton exchange events. Our results hold for [polyU·polyA] duplexes (U and A are bases paired by means of Watson-Crick H-bond interactions). We prove that the density of domain walls is increased by the same phonon excitations which would enhance proton exchange with the solvent. The identity of the catalytic groups in the process is established.

The design of experiments which would serve as probes for nonlinear excitations along nucleic acid chains remains elusive [1]. Thus, the validity of models for coherent wave excitations travelling along the helical macromolecular structures [2, 3] remains an open question. In this work we implement a statistical mechanical model for coherent solitary-wave excitations which is amenable to experimental testing. The model assesses the role of soliton-induced conformational changes in the elucidation of the identity of molecular groups responsible for the proton transfer catalytic activity of RNA. The situation requires a theoretical understanding cast in terms of nonlinear temperature-dependent collective modes and can be described as follows: certain double-stranded RNA species, such as [polyU·polyA] (the pairing between the bases U and A being of Watson-Crick type) are capable of exchanging protons with the solvent in a regime which is far from denaturation conditions [4]. The puzzling aspect is that the protons exchanged with the solvent are precisely those involved in Watson-Crick H-bond pairing, suggesting that some sort of pre-melted region or 'bubble' within which the proton exchange event takes place should occur in the helical structure. These local domains seem to be endowed with an abnormally long lifetime (in certain cases of the order of seconds) and their very nature remains obscure [5]. In this respect, a scenario in which some sort of nonlinear excitation is able to concentrate energy in localised regions of the helix seems to be suggestive and relevant. However, in order to give shape to the idea, we need to implement a model where a topological soliton, that is a discommensuration, travelling along the sugar-phosphate backbone is coupled to the torsional motion of the bases whose protons become exposed to the solvent once the pre-melted region is formed. Thus, our strategy consists in defining a model Hamiltonian involving two relevant variables per monomeric unit (a monomeric unit comprises a phosphate, a sugar and a base residue). These variables depend on x, the contour parameter indicating the position on the chain. They are: (a) the pseudorotational angle $u = u(x, t)$ which characterises the sugar pucker conformation and (b) the

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torsional angle $\phi = \phi(x, t)$, determining the swinging of the base along the sugar-base glycosidic bond, away from the equilibrium position in the pairing.

The identity of the proton transfer agents within an RNA duplex has not been established so far. Nevertheless, we shall argue that the catalytic activity of RNA can be effectively coupled to the kink induced by a soliton, thereby altering the rate of proton exchange with the solvent. The relevant catalytic mode for proton exchange is displayed in figure 1. The conformational transition between the two sugar puckers leads to the activation of the 2′-hydroxyl group and the concomitant formation of the alkoxide. This conformational change in the ribose is the discommensuration produced by the kink travelling along the chain backbone. A direct inspection of figure 1 reveals that the conformational change induces a keto-enol tautomerisation in the uracil (U) directly attached to the ribose. In that way, the soliton is coupled to the exchange of the uracil N3-proton with the solvent proton. Several experimental facts [4] support the scheme proposed in figure 1. They are:

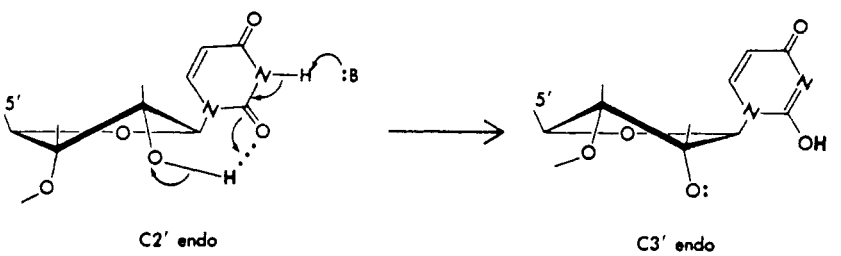

Figure 1. Coupling of the conformational change in the ribose with a proton exchange event involving the labile uracilic proton. The nucleophilic 2′-hydroxyl of the ribose is activated due to the interaction between the backbone sugar residue and the base. The symbol ':B' denotes the nucleophilic part of a solvent molecule, that is, the region which is able to accept a proton from the RNA.

(*a*) the uracil N3–H proton exchanges appreciably faster than the proton for the conjugated base;

(*b*) the U base swings out while the conjugated A base remains more or less stacked within the duplex;

(*c*) the proton exchange process in the RNA species is enhanced with respect to an analogous process in the DNA duplex [poly(dA)·poly(dT)]. Suggestively, the activation barrier for interconversion between the two puckers in the RNA ribose is higher than in the DNA deoxyribose [4–6].

The soliton model in DNA has been extensively studied [2], however, we would like to emphasise that an analogous model for the RNA species brings up the possibility of additional probes. This assertion will be justified once we have proved that it is feasible to activate the 2′-hydroxyl of the ribose by means of the soliton, thus confirming its direct participation in a proton exchange event. For clarification let us consider the Φ^4 model widely used in condensed matter physics. This model is adequate when structural phase transitions are inherent to the sugar ring and represent conformational changes. In our specific case of interest, the transition is the molecular rearrangement C2′-endo–C3′-endo, modelled by a site-dependent double-welled local potential in the variable u. Each of the wells corresponds to a different conformational isomer. When the action is given as in the Φ^4 model, large amplitude solutions in the form of solitary

kinks reverse the phase of the system. The uniqueness of RNA resides in that the topological soliton has an additional effect which is normally attributed to non-topological solitons exclusively engaged in energy transfer.

In order to explore the theoretical possibilities of these ideas, we shall introduce the following model Hamiltonian:

$$H_T = A_0 + B_0 + V + A_1(t) = H + A_1(t). \tag{1}$$

In (1), the first two terms are Hamiltonians which govern the dynamics of the sugar pucker and the swinging of the base respectively. V describes a coupling between these two modes and A_1 is an external stochastic field. $A_0 = A_0(u)$ is given by

$$A_0 = \int \frac{dx}{l}\left[\frac{p(x)^2}{2m} + \frac{A}{2}u(x)^2 + \frac{B}{4}u(x)^4 + \frac{mc_0^2}{2}\left(\frac{du}{dx}\right)^2\right]. \tag{2}$$

Here l is the lattice spacing and the contour variable x locates a sugar residue along the chain: $x = x_j = jl$; c_0 is the speed of sound and $p(x)$ is the momentum conjugate of the variable $u(x)$. The constants A and B determine the quartic potential which governs the sugar conformational changes. A is negative and B positive and they are chosen so that the depth $v = |A^2|/4B$ of the local potential wells ($u = \pm u_0$) corresponds to a barrier of 3 kcal between the two stable sugar configurations $u = +u_0$ (C3′-endo) and $u = -u_0$(C2′-endo) [6].

B_0 is the contribution from the swinging of the base which involves only the torsional angle ϕ along the glycosidic bond between the base and the sugar pucker. This Hamiltonian contains the usual kinetic energy term and an elastic contribution, $K\{\partial\phi/\partial x\}^2$, that represents the stacking of the bases. The elasticity constant K should be estimated from the statistical thermodynamics of the separable Hamiltonian made up of the first two terms in (1): a reasonable denaturation temperature is obtained fixing K at 8×10^{-4} eV deg^{-2} (cf [2]).

The statistical mechanics which stem from B_0 are trivial insofar as only a phononic response is plausible. On the other hand, the statistical mechanics stemming from the contribution A_0 may lead to a nonlinear response in the form of a domain wall of thickness $2[2]^{1/2}\xi = L$. The parameter ξ determines the familiar form of the soliton solution [7] for the dynamics determined by A_0:

$$u = u_0 \tanh[(x - vt)/2^{1/2}\xi] \tag{3}$$

$$\xi^2 = m(c_0^2 - v^2)/|A|. \tag{4}$$

A partition function associated with a Hamiltonian equivalent to A_0 has been obtained by making use of the transfer operator technique [7]. The same technique has been implemented by the author to study phase transitions in polymer physics [8].

We now consider a far more complicated situation which arises when the coupling term V is added to the previous contributions. This term arises from the coupling between the conformational change in the sugar and the swinging of the base, as suggested by the chemistry depicted in figure 1. Thus, we adopt the following expression:

$$V = Ju\phi \tag{5}$$

where the coupling constant J will be determined once we have elucidated the thermodynamics of the full non-separable Hamiltonian H_T. This strategy will find its justification once we have shown that those phononic excitations which are responsible

for the enhancement of the proton-exchange activity are also responsible for increasing the density of domain walls. Thus, we shall adjust J to match the bands which have been found experimentally to be most favourable in order to enhance the localised melting in a helix.

The stochastic source $A_1(t)$ is introduced to simulate the full spectrum of an external fluctuating field. This field is comprised of extended mode excitations which result from random collisions with the solvent molecules and counterions. We adopt for the field the general form:

$$A_1(t) = \sum_{\omega} e^{-i\omega t} A_1(\omega) \tag{6}$$

where ω is the frequency of a particular extended normal mode. Thus, the contribution of each individual Fourier component, $A_1(\omega)$, to the creation of domain walls will be assessed. Of particular significance are those wavelengths approaching the actual thickness of the domain walls or kinks.

The dynamics for the full Hamiltonian is probably intractable unless we introduce the *a priori* restriction that the coupling term V can be treated perturbatively. The subsequent results will justify this assumption. In order to examine the response of the system to the fluctuating field, we shall adopt the density operator representation to study the evolution of the system. Denoting by $\rho = \rho(t)$ the density operator for the system, the partition function Q is

$$Q = \mathrm{Tr}\, \rho. \tag{7}$$

Since we are interested in the effect of the soliton which propagates in the u-space, we find it convenient to introduce the variable σ, defined by

$$\sigma = \mathrm{Tr}_{\phi}\, \rho \tag{8}$$

where Tr_{ϕ} denotes the trace operation over the torsional angle variable only. We shall present the results of a first-order renormalisation, that is, in the lowest Born approximation to the collision superoperators. This procedure gives

$$\frac{d}{dt}\sigma_1(t) = -i\tilde{A}_0\sigma_1(t) + \tilde{C}_0(t, \{\sigma_1\}) - i\tilde{A}_1(t)\sigma(0) + D_0(t) \tag{9}$$

where σ_1 denotes the linear part of σ, and the letters with tildes symbolise superoperators associated with the corresponding terms in the full Hamiltonian. The lowest Born approximation to the collision operator, $\tilde{C}_0$, is given by

$$\tilde{C}_0(t, \{\sigma_1\}) = -\mathrm{Tr}_{\phi}\tilde{V} \int_0^t d\tau \exp(-i\tilde{H}_0\tau)\, \tilde{V} f(B_0)\sigma_1(t-\tau) \tag{10}$$

where $H_0 = A_0 + B_0$ and $f(B_0) = \exp(-\beta B_0)/\mathrm{Tr}\{\exp(-\beta B_0)\}$.

The last term in (9) is given by

$$D_0(t) = -\mathrm{Tr}_{\phi}\tilde{V} \int_0^t d\tau \exp(-i\tilde{H}_0\tau)\tilde{A}_1(t-\tau) f^{(1)} \tag{11}$$

where $f^{(1)}$ is the lowest order term in the expansion of $f(H)$ in powers of V. This procedure merits a digression. We have assumed throughout the paper that V can be treated perturbatively as a contribution of the total Hamiltonian; therefore, a Taylor expansion of $f(H)$ in powers of V is feasible.

At this point we are in a position to analyse the response of the system to the generic fluctuating field. For this purpose we find it convenient to introduce the density operator s, obtained from σ_1 by substracting the part of $f(H)$ which is V-independent. Thus, the norm $|s|$ measures the nonlinear response as given by the density of the one-dimensional gas of domain walls. We could then analyse the dispersion of $|s|$ by plotting this quantity against ω. However, we find it more revealing to plot $|s|$ against the wavelength given in units of L (the reader should recall that L is the width of the domain wall). The wavelength can be obtained from ω since we have already introduced the speed of sound in (2). This representation is adopted in figure 2. The plot is obtained making use of (9) combined with the statistical mechanics for H_0 which are obtained explicitly from the Φ^4 model of Krumhansl and Schrieffer [7].

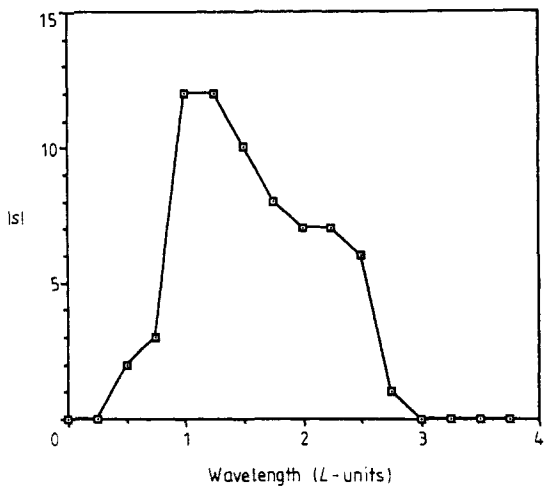

Figure 2. Response of the system to the generic fluctuating field. The abscissa is the wavelength of the stochastic source and scales with the thickness of the domain walls produced in the backbone of RNA. The ordinate gives the norm of the density operator s.

The main result which follows after direct inspection of figure 2 is that the phononic excitation is most effective in increasing the density of walls when the wavelength gets closer to the thickness of the wall. The results suggest that extended modes detectable in low-frequency Raman scattering [9] might be effective in enhancing the proton exchange activity. In particular, those modes lying in the range 85–100 cm^{-1} are crucial for J in the range $2.4\text{–}2.8 \times 10^{-6}$ eV deg^{-2}. The importance of those bands has been emphasised in the context of energy transfer for DNA transcription [9]. Similarly, the progressive melting of interchain secondary structure between replica and template during RNA replication [10] demands the participation of nonlinear modes analogous to those studied in this work. This follows from the fact that extended mode excitations which cause a higher density of domain walls are precisely those responsible for the enhancement of bubble formation in helical structures. We interpret such results as conclusive evidence in support of the view that a topological soliton is able to induce a proton exchange event at the particular site of the kink. The probability of the event depends exclusively on the strength of the coupling of the sugar discommensuration to the isomerisation of the base.

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