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Dynamics of electronically excited cytosine stacks

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Abstract. We have studied the dynamics following a localized excitation of a molecule in a chain of stacked ring-shaped aromatic molecules. As model system we have chosen a cytosine stack, since our study is based on recent ideas on the mechanism for the creation of double-strand breaks in DNA which require energy transport through DNA. After a π–π^*-excitation a cytosine molecule increases the size of its ring. The excitation and the accompanying geometrical changes are coupled to the electronic system of the chain in a non-linear manner. As a mathematical model for the π-electrons we use a tight-binding *ansatz* with parameters taken from *ab initio* Hartree–Fock calculations. We found that initially an excitation is localized on one molecule and that these localized excitations move in a random manner through large parts of the chain. Although this phenomenon most probably is not a solitary wave, the non-linear quasiparticles found in our system transport energy along the chain.

1. Introduction

It is well known that polymeric systems, exhibiting non-linear forces, can support quasiparticles which are localized on a limited number of sites. Most types of these quasiparticles are able to move through large parts of a system without changing their form very much. Depending on the features of these quasiparticles, like the number of states that they create in the fundamental gap of the system or their charges, they are called e.g. solitary waves, polarons, or bipolarons In particular the creation of solitons, having infinite lifetimes, or solitary waves, having finite lifetimes, is invoked in the explanation of a large variety of physical phenomena. Here we want to list just some examples, like ferromagnetism [1], antiferromagnetism [2], phase changes [3], charge transport in *trans*-polyacetylene [4], dynamics of the sugar–phosphate backbone of DNA (deoxyribonucleic acid) [5], and the dynamics of the nucleotide base stacks of DNA [6]. The first observation of the formation of a solitary wave was published in 1844 [7], where in a channel near Edinburgh a water wave was formed which travelled through the channel without changes in its form. Further, the transport of light pulses through fibres happens in a solitary manner [8] and solitons could also be observed in chains of Josephson junctions as fluxons [9]. Finally we want to mention the Davydov soliton [10] which is postulated to be responsible for energy and signal transport in proteins.

An interesting application of non-linear dynamics to DNA is in the investigation of pre-melting phenomena, where the backbones of the two chains are simulated as chains of coupled harmonic oscillators and the hydrogen bonds between them by Morse potentials [6, 11]. Our work on DNA is based on ideas coming from the field of cancer research. Carcinogenesis is caused mostly by three different types of agent, namely by viruses,

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chemical carcinogens and radiation, where chemicals are responsible for up to 80% of all tumours [12]. In principle there are several ways for a cell to become malignant. One of them, e.g., is a point mutation in DNA [13]. Other and more frequent mechanisms consist in a removal of blocking proteins from oncogenes [14, 15], translocations [16–18] or amplifications of genes. All these cases have in common that an oncogene is activated or overactivated, so the oncoproteine coded by it occurs in much larger concentrations in the cell than is usual. However, the removal of blocking proteins from DNA cannot be explained by local effects [19]. Therefore several long-range mechanisms were proposed to explain such events [20]. One of these mechanisms is the creation of conformational solitary waves from initial geometrical distortions in the base stacks due to the attack of bulky carcinogens [21–24]. The numerical study of such solitary waves, both in model systems and in DNA itself, was the subject of several previous papers [25–28] and their existence in stacks of molecules, including the nucleotide bases, was numerically confirmed.

The present work is based on a hypothesis, developed by Ladik [19], [27], [29–31], to explain the experimentally observed number of double-strand breaks (DSB) in DNA as function of the (ionizing) radiation dosage (linear plus quadratic dependence). Note that a more complete review of experimental and theoretical developments in the field of carcinogenesis was published recently [32], where also the concepts mentioned here are explained in more detail. It is very improbable that, following a single-strand break (SSB) by one hit of radiation on DNA, the second hit necessary to cause the DSB will occur in the same region of the system. On the other hand, if a single particle caused both breaks, the above-mentioned DSB–dose curve had to be a straight line. Thus for explanation one needs again a long range mechanism (see, e.g., [30]). In this case the considerations start from the experimentally well known fact, that ring-shaped molecules containing π-electron systems, e.g. benzene (see [29–32] for references on experimental results), increase their size in excited states. Thus one can postulate that due to the non-linear interaction of such a geometrical distortion with the change of the electronic system, solitary waves could be formed. One could think here of two different effects: (i) the molecule returns after the excitation into its electronic ground state, but keeps the geometry of the excited state, which due to the non-linear interactions can move along the chain; and (ii) the electronic excitation itself together with its accompanying geometrical change can move. In this way the energy could be transported from the site of the second hit of radiation to the site of the initial SSB, which acts as a distorted region were the quasiparticle most probably would lose its energy and thus could create the final DSB. Finally, caused by such a DSB, cancer could be initiated if so-called (cell-duplication-hindering) antioncogenes are coded in the lost parts of the DNA molecule.

In this work we study numerically the question of the existence of these postulated non-linear quasiparticles in a model system consisting of a chain of stacked ring-shaped molecules containing an aromatic π-electron system. Since it is technically possible to perform the necessary calculations directly on the nucleotide bases which occur also in DNA, there is no reason to restrict ourselve to models like benzene. Therefore we have chosen a stack of cytosine molecules in the same geometry as can be found in B DNA for our calculations. However, one has to keep in mind that additional interactions of cytosine with the sugar–phosphate backbone and via hydrogen bonds with the second strand are neglected in our model. We will return to this point in the conclusion.

2. The model

As a simple model system for one strand of DNA we use a stack of cytosine molecules in B DNA geometry. Assuming one geometrical degree of freedom per molecule and σ–π-separation, the potential energy of the stack can be written as

$$U = E_{\text{core}}(f_1, ..., f_N) + E_\pi(f_1, ..., f_N). \tag{1}$$

Here N denotes the number of cytosine molecules in the stack, and f_i the (generalized) coordinate of molecule number i. f_i is defined through the ground- (G) and excited- (E) state geometries of the cytosine monomer (see below). For the kinetic Energy T at time t of one cytosine molecule one obtains

$$T(t) = \frac{1}{2}\sum_{j=1}^{M}(\dot{x}_j^2(t) + \dot{y}_j^2(t) + \dot{z}_j^2(t))m_j. \tag{2}$$

M is the number of atoms in one cytosine molecule, x_j, y_j and z_j are their cartesian coordinates and m_j is the mass of atom j. Assuming for each atom only movement on the connecting lines between G and E, it is possible to define the generalized coordinate $f(t)$:

$$x_j(t) = x_j^G + (x_j^E - x_j^G)f(t) \qquad \dot{x}_j(t) = (x_j^E - x_j^G)\dot{f}(t). \tag{3}$$

$f = 0$ corresponds to the ground-state geometry, and $f = 1$ to the excited-state geometry. The kinetic energy now becomes

$$T(t) = \frac{1}{2}\sum_{j=1}^{M}\left[(x_j^E - x_j^G)^2 + (y_j^E - y_j^G)^2 + (z_j^E - z_j^G)^2\right]m_j\dot{f}^2(t) \tag{4}$$

and the effective mass is thus defined as

$$m_{\text{eff}} = \sum_{j=1}^{M}\left[(x_j^E - x_j^G)^2 + (y_j^E - y_j^G)^2 + (z_j^E - z_j^G)^2\right]m_j. \tag{5}$$

G and the geometry of B DNA were taken from [33]. To obtain a qualitative estimate of the form of the geometry of E, CAS-SCF calculations with geometry optimization on the cytosine monomer were performed using the GAUSSIAN 92 program package [35]. The active space of the configuration interaction was chosen to consist of ten electrons in eight atomic orbitals, the complete π-system of cytosine in a minimal basis set (STO-3G) [35]. We want to note at this point that we cannot choose the first π-excitations, because in this case extra-ring C–N or C–O bonds would increase their length. We consider the changes in the interactions between two stacked molecules to be rather small if only an extra-ring bond length is varied. Therefore, we do not expect that from such a distortion non-linear quasiparticles could be formed. A change in the size of the ring can only be obtained by a $\pi \rightarrow \pi^*$-excitation between orbitals with their largest coefficients in the ring system. For the second excited state we found a change in the ring perimeter from 8.38 Å to 8.69 Å ($\Delta = 0.31$ Å). This result is in the same range as the experimentally observed changes for benzene (from 8.39 Å to 8.62 Å, $\Delta = 0.23$ Å) [34].

$E_\pi(f_1, ..., f_N)$ was modelled with a tight-binding (Hückel) *ansatz*:

$$\underline{\underline{\beta}}(f_1, ..., f_N)c_k(f_1, ..., f_N) = \epsilon_k(f_1, ..., f_N)c_k(f_1, ..., f_N) \tag{6}$$

$$E_\pi(f_1, ..., f_N) = \sum_{k=1}^{n_{\text{occ}}} o_k\epsilon_k(f_1, ..., f_N), \tag{7}$$

where ϵ_k is the kth eigenvalue, c_k the kth eigenvector, n_{occ} the number of occupied π-orbitals and o_k the occupation number of orbital k. Assuming next-neighbours interactions, $\underline{\underline{\beta}}(f_1, ..., f_N)$ has a block-matrix structure: diagonal blocks for the π-orbitals of the cytosine monomer and off-diagonal ones for the orbitals describing the interactions in the dimer. As parameters for the Hückel matrix we use the converged π-electron matrix elements of Fock matrices from cytosine monomer and dimer calculations (B DNA geometry) determined with the help of RHF (restricted Hartree–Fock, STO-3G basis set) calculations [35]. To get the matrix elements in an analytic form as a function of the coordinates f_i, we performed 100 RHF calculations varying the geometries in the range $f_1, f_2 \in [-2, 4]$. The π-electron elements of the resulting Fock matrices were fitted to polynomials of fifth degree in f_1, f_2 using a least-squares algorithm supplied by the NAG library [36]. The resulting dimension of the Hückel matrix for a stack of N cytosine molecules $\underline{\underline{\beta}}(f_1, ..., f_N)$ is—using the $N_\pi = 8$ π-orbitals per molecule from the STO-3G RHF calculations—$N_{matrix} = N \times N_\pi$.

The core energy E_{core} is also calculated assuming next-neighbours interactions. It is determined in a way in which the energies of the cytosine monomer $E^M_{RHF}(f_1)$ and dimer $E^D_{RHF}(f_1, f_2)$ from the RHF calculations are reproduced:

$$E^D_{core}(f_1, f_2) = E^D_{RHF}(f_1, f_2) - E^D_\pi(f_1, f_2) \tag{8}$$

$$E^M_{core}(f_1) = E^M_{RHF}(f_1) - E^M_\pi(f_1) \tag{9}$$

which implies that

$$E_{core}(f_1, ..., f_N) = \sum_{i=1}^{N-1} E^D_{core}(f_i, f_{i+1}) - \sum_{i=2}^{N-2} E^M_{core}(f_i). \tag{10}$$

$E^M_{core}(f_1, f_2)$ and $E^M_{RHF}(f_1)$ are also fitted to polynomials of fifth degree in f_1, f_2.

The next step is to set up the dynamics of the system via the Lagrangian formalism:

$$L = T - U \Rightarrow \frac{d}{dt}\frac{\partial L}{\partial \dot{f}_i} = \frac{\partial L}{\partial f_i} \tag{11}$$

$$m_{eff}\ddot{f}_i = -\frac{\partial E_{core}(f_1, ..., f_N)}{\partial f_i} - \frac{\partial E_\pi(f_1, ..., f_N)}{\partial f_i}. \tag{12}$$

The derivatives of $E_{core}(f_1, ..., f_N)$ are given analytically through the fitted polynomial. To obtain the derivatives of $E_\pi(f_1, ..., f_N)$, the variational principle and the properties of the charge-density-bond-order-matrix given by

$$P_{rs} = \sum_{i=1}^{N_{matrix}} o_i c_{ri} c_{si}$$

are exploited using the derivation given in [37]:

$$\frac{\partial E_\pi(f_1, ..., f_N)}{\partial f_i} = \sum_{r,s=1}^{N_{matrix}} P_{rs}(f_1, ..., f_N)\frac{\partial \beta_{rs}(f_1, ..., f_N)}{\partial f_i} \tag{13}$$

This shows that—compared to a strictly classical model with next-neighbour interaction—the force acting on molecule i is depending not only on the neighbouring monomers $i-1$ and $i+1$, but also (parametrically) on the coordinates of all molecules in the stack. Also it is possible to include electronic excitations of the stack via the Hückel model of the π-electrons. Thus, the treatment of the cytosine stack is an adiabatic one in the way that the changes in the electronic structure of the molecule (due to geometrical changes and/or electronic excitation) have an effect on the energy gradients of the atomic centres.

For the numerical solution of the resulting nonlinear system of differential equations we used a simple one-step procedure. The starting point is a set of initial coordinates $f_i(t_0)$, velocities $\dot{f}_i(t_0)$ at time t_0, and a certain electronic state of the π-system specified by the occupation numbers o_i. Then the energies E_π and E_{core} and their gradients are calculated, i.e. the Hückel problem has to be solved in each timestep. The coordinates and velocities for $t_0 + \Delta t$ are

$$\dot{f}_i(t_0 + \Delta t) = \Delta t\, \ddot{f}_i(t_0) + \dot{f}_i(t_0) \tag{14}$$

$$f_i(t_0 + \Delta t) = \Delta t\, \dot{f}_i(t_0) + f_i(t_0). \tag{15}$$

More involved procedures such as the Runge–Kutta method were also tested, but proved to have no advantage over the one presented in our case. To track the accuracy of the solutions, the total potential and kinetic energy of the stack were monitored.

3. Results and discussion

3.1. Static properties

The π-energies calculated with the Hückel model are shown in figure 1 for a stack of 30 cytosine molecules. In the ground-state conformation, one gets more or less narrow bands consisting of 30 states with large gaps in between. Changing the coordinate f_i of one molecule in the stack has the effect that one state is pushed out of the band into the gap. This reflects the fact that in our model geometrical changes alter the Hückel matrix and thus the electronic structure of the stack.

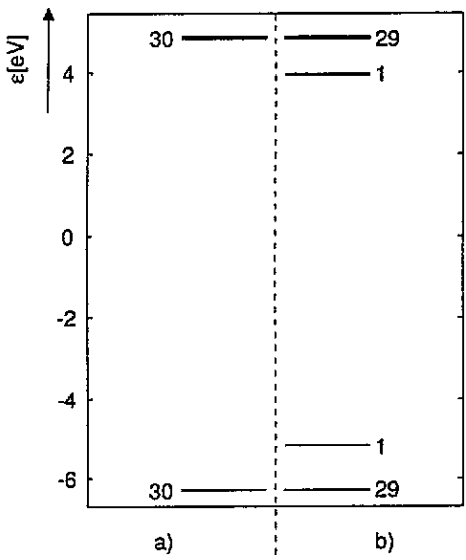

Figure 1. Excited energy levels ϵ (in eV) of a stack of 30 cytosine molecules as calculated with our Hückel *ansatz*. (a) All molecules in the ground-state conformation. (b) Molecule 15 in the excited-state conformation ($f_{15} = 1$); all others with ground-state geometry. The numbers by the lines indicate the numbers of states in the corresponding bands.

To visualize some of the properties of the potential surface $U(f_1, ..., f_N)$, we made 'cuts' in such a way, that 28 or 29 coordinates f_i are kept fixed and two or one are varied. The resulting potential energies are shown in figure 2, (a) and (b). Here it is very important to observe the difference between ground- and excited-state surfaces. In the ground state one gets a potential with one minimum having a large harmonic term. Changing to an excited state, the potential surface is cut into branches with local minima. This is quite

interesting because it shows that in the case of excitation there is not just a change in the position of the minimum: the interaction changes and shows a more nonlinear characteristic, which can especially be seen in the plots of the derivatives (figure 2, (c) and (d)).

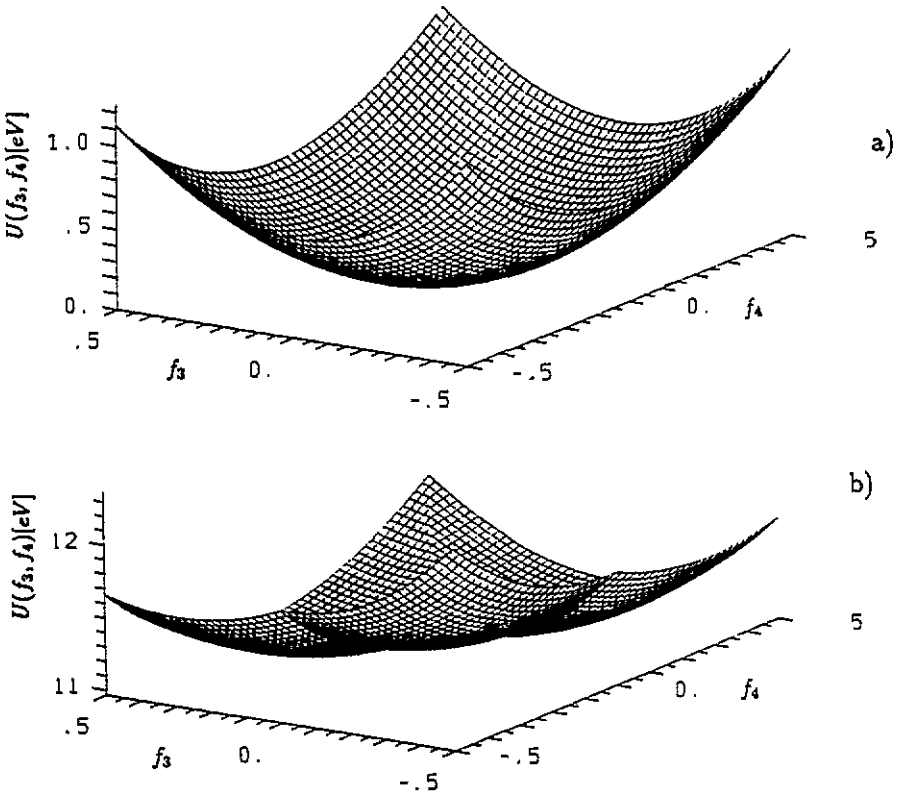

Figure 2. (a), (b) The central part of the energy surface $U(f_2, f_3)$ for a stack of 30 cytosine molecules. U is in eV, f_2, f_3 are the generalized coordinates of molecules 2, 3. ((a) Ground state. (b) Excited state.) (c), (d) $\partial E_{\text{core}}(f_3, 0)/\partial f_3$ (— – —), $\partial E_\pi(f_3, 0)/\partial f_3$ (— · —) and $\partial U(f_3, 0)/\partial f_3 = \partial E_{\text{core}}(f_3, 0)/\partial f_3 + \partial E_\pi(f_3, 0)/\partial f_3$ (——) for a stack of 30 cytosine molecules as a function of f_3. ((c) Ground state. (d) Excited state.) Inset: $\partial U(f_3, 0)/\partial f_3$.

3.2. Simulations

We want to present five simulations performed with this model.

(i) The system is in the electronic ground state with molecule 18 having an initial perimeter 3.7% larger than in the ground-state conformation ($f_{18} = 1$).

(ii) The system is excited with 4.7 eV, the ring perimeter of the cytosine molecule number 15 is 3.7% larger than in the ground-state conformation ($f_{15} = 1$).

(iii) The system is excited with 4.7 eV, the ring perimeter of the cytosine molecule number 3 is 3.7% larger than in the ground-state conformation ($f_3 = 1$).

(iv) The system is excited with 9.5 eV, the ring perimeter of the cytosine molecule number 15 is 9.9% larger than in the ground-state conformation ($f_{15} = 2.5$).

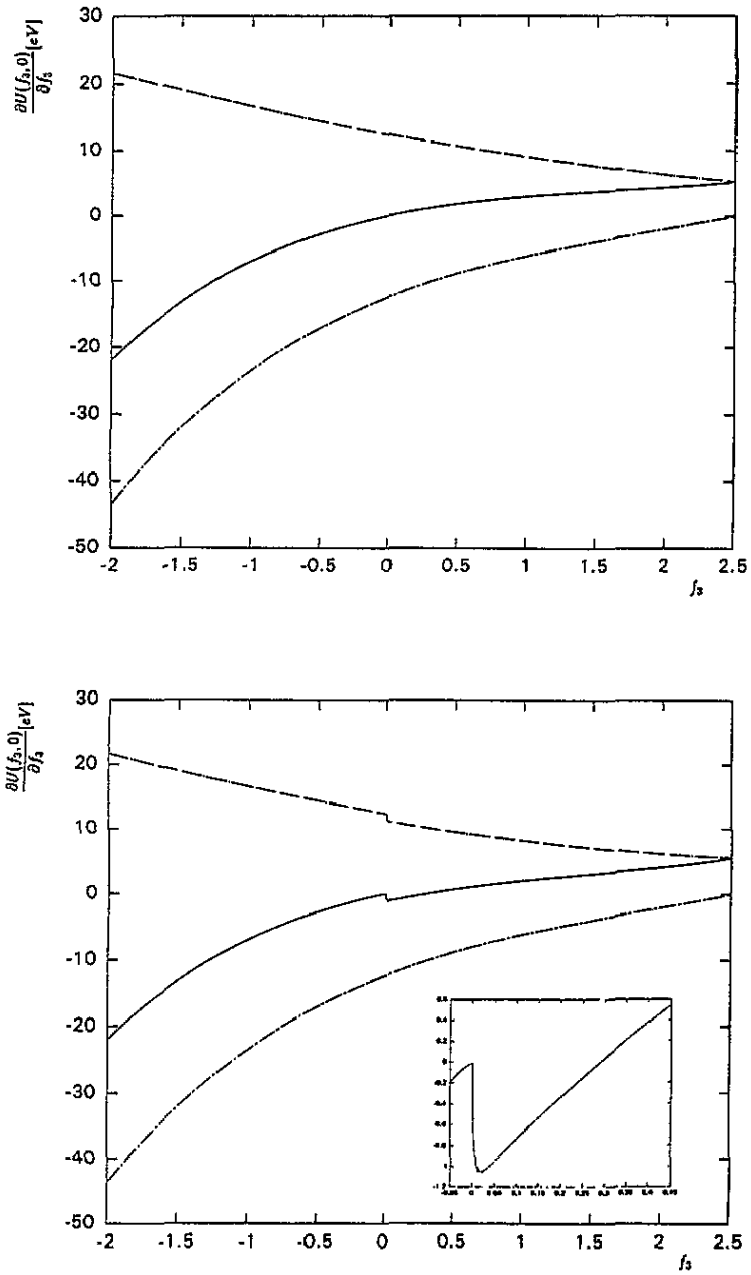

Figure 2. (Continued)

(v) The system is excited with 9.5 eV, the ring perimeter of the cytosine molecule number 3 is 9.9% larger than in the ground-state conformation ($f_3 = 2.5$).

The excitation energies were achieved through appropriate scaling of the Hückel parameters; consequently, the core energy was also scaled to keep the minimum of the ground-state potential surface at the G conformation. The change in geometry in simulation 2 and 3 corresponds to the one calculated with CAS-SCF. The cases 4 and 5 were chosen to

model a higher excitation with a correspondingly larger initial change in geometry. It is of course also possible to perform adiabatic calculations in the sense that only the electronic state of the system is given as a starting position, where the excitation is observed to localize very fast. We use the initial geometry change to force the excitation to be localized at a certain molecule, as in the case of radiation hitting one molecule in the stack. We monitored the change of the geometries, the local kinetic energy, the sum of the squares of the singly occupied excited MO coefficients of each molecule (EXMO) (in case 1 the sum of the squares of the HOMO coefficients). The relative errors of the potential energy at the beginning compared to the sum of potential and kinetic energies during the simulation are less than 3%.

(i) **Case 1: ground state.** In this case we model the situation, where—after an initial excitation—one molecule returns to its electronic ground state, keeping the excited-state conformation. We then observe how the molecule adjusts itself again to the ground-state geometry. Here one gets (nearly) harmonic vibrations of the molecule which had an initial geometrical change. The local kinetic energy as well as the HOMO coefficients follow this motion (see figure 3). This corresponds to test calculations made without the Hückel *ansatz* for the energy: the molecule with the initial geometry $f_{15} \neq 0$ vibrates without having any effect on the other molecules, since the mechanical coupling between the stacked layers is very weak. This is also to be expected from the (mainly) harmonic potential surface of the ground state. After long times—probably on the nanosecond scale—the vibrational energy will disperse.

(ii) **Cases 2 to 5: excited states.** The general feature of these simulations is, that the oscillation does not stay at the position of the initial geometrical distortion, but that the peaks of the coordinate, kinetic energy and the EXMO coefficients are changing their position widely during the time examined (cf figure 4–figure 7), but no smooth movement of the excitations is observed.

To go into detail, in calculation 2 (figure 4) the whole chain vibrates after 200 fs but there is no simple dispersive behaviour. In contrast, the peaks of the geometry, kinetic energy and the EXMO coefficients are hopping between positions 15 (start), 11 and 21 during the first 5 ps. After that, the peaks of the kinetic energy start to flatten, and the energy becomes distributed over the chain: but the perimeter change still has localized peaks around the initial value even after 10 ps, and the heights of the peaks of the kinetic energy are still about 10% of the ones around 1 ps. The position of the excitation, shown by the EXMO coefficient, is always very localized and correlated with the size changes of the cytosine rings.

Calculation 3 (figure 5), having the same initial potential energy as calculation 2, shows very high peaks in the kinetic energy hopping from position 3 to 19 during the first 5 ps. This can also be observed for the EXMO coefficients.

The examples with higher excitation energy, 4 and 5 (figures 6, 7), show a far smaller tendency to spread the kinetic energy over the chain: in example 4 (figure 6), the peaks of the kinetic energy develop branches, hopping from 15 to 22 to 29 and then back to 8 during the first 4 ps, not losing not very much height. After 10 ps, the kinetic energy at the initial geometrical distortion has nearly vanished. It is now concentrated at positions 5, 8 and 25, each of them having roughly one third of the heights of the initial peaks. The same behaviour can be found for the geometry and the EXMO coefficients. In calculation 5, the kinetic energy starts with peaks at position 3, then it develops peaks at 5 and a smaller peak at 29; but overall, the kinetic energy develops very slowly from the initial peak to the other side of the stack and about 12 ps elapses before a peak around position 25 starts to emerge.

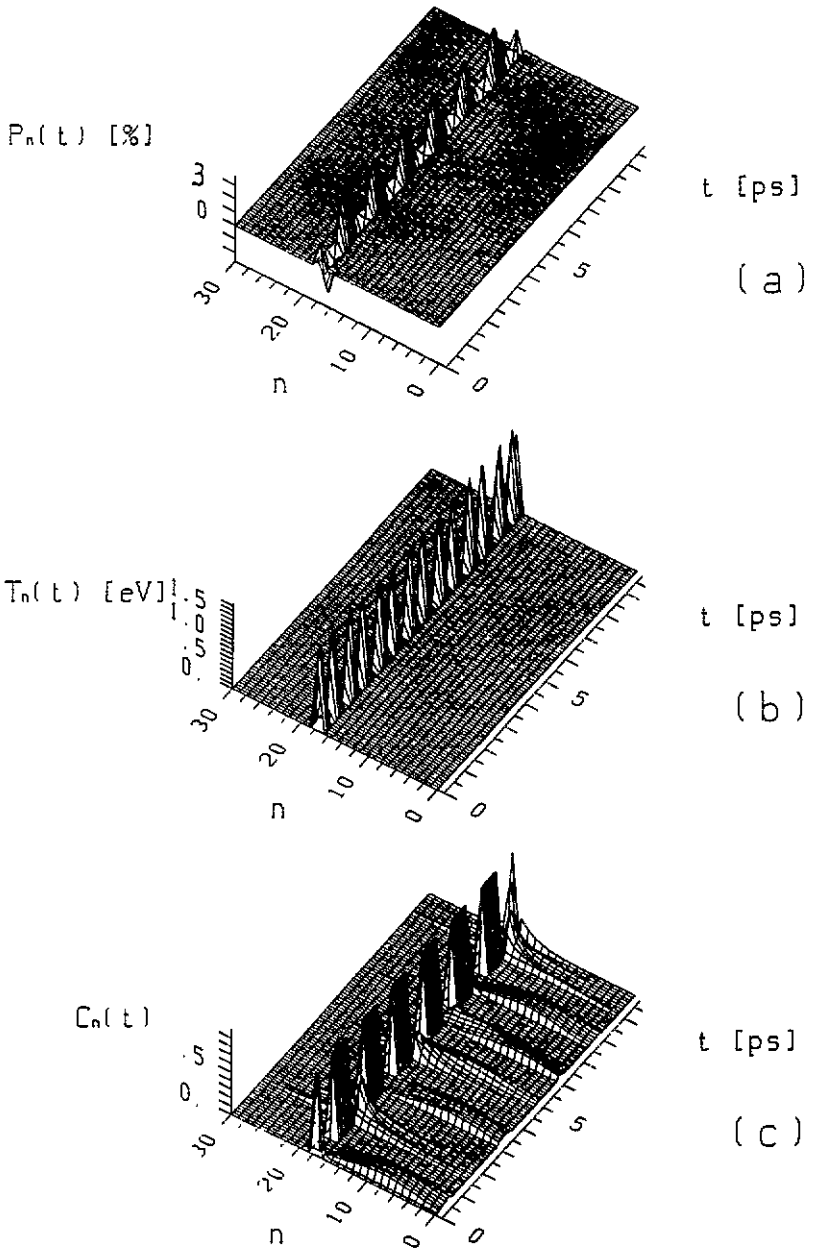

Figure 3. Simulation on a stack of 30 cytosine molecules for the electronic ground state of the system. The initial ring size of molecule number 18 is 3.7% larger than in the ground-state conformation. (a) The relative change of the ring perimeter $P_n(t)$ (in %) as a function of molecule number n and time t (in ps). (b) Local kinetic energy $T_n(t)$ (in eV) as a function of molecule number n and time t (in ps). (c) $C_n(t) = \sum_{m=1}^{N_\pi} |c_{n_{\text{occ}},(n-1)N_\pi}|^2$, the sum of the squares of the HOMO coefficients as a function of molecule number n and time t (in fs).

4. Conclusion

The main feature of the model calculations presented is that, in the case of an electronically excited cytosine stack kinetic energy is transported in a random way to other than the initial

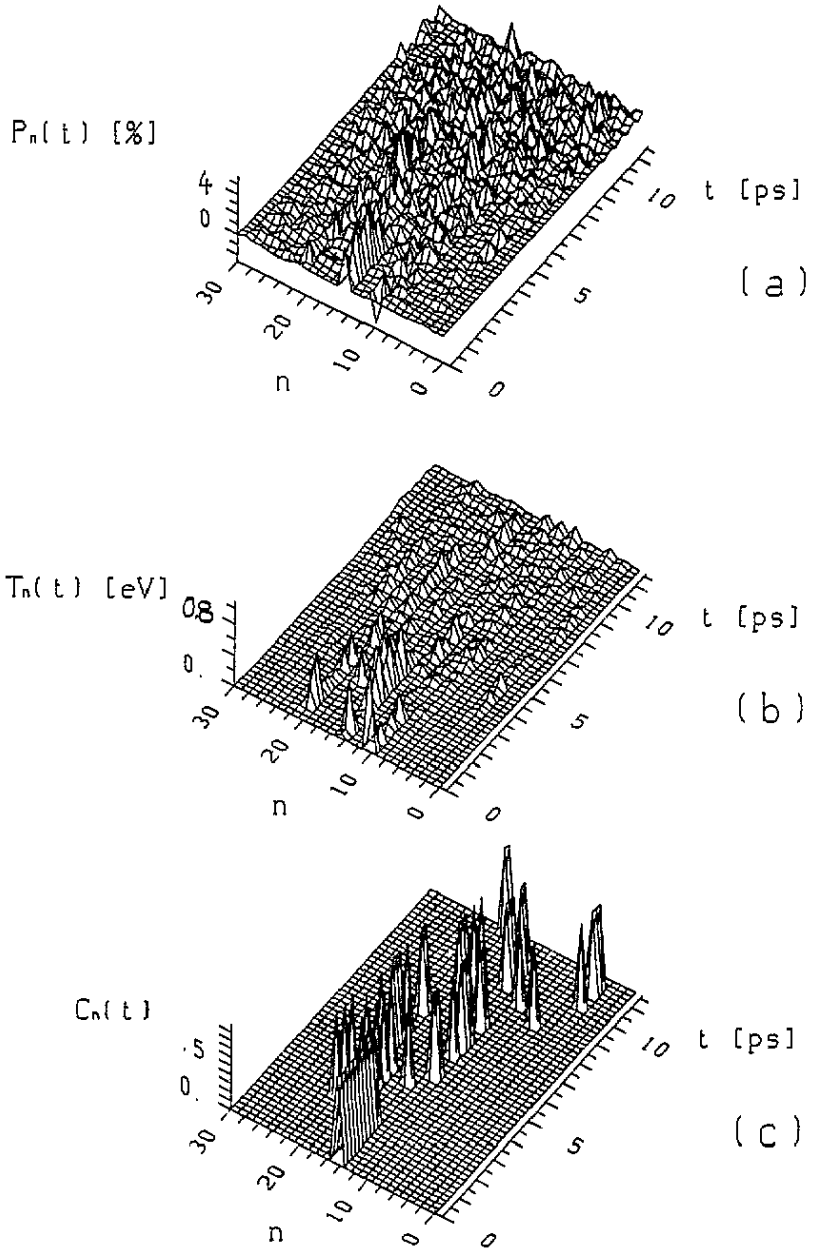

Figure 4. Like figure 3, but with an excitation energy of 4.7 eV. (c) The sum of the excited-state coefficients.

positions with very little energy loss over a considerable timescale. The indeterministic nature of the hopping of the excitation is due to the fact that geometrical changes have a large effect on the molecular orbitals causing sudden changes of their localization properties. The movement of the excitations would show a much smoother characteristic, if we were to change to a description which is not as strictly adiabatic as ours. This could be done by applying *ansatz* states such as that of Davydov, which are formed as products of a

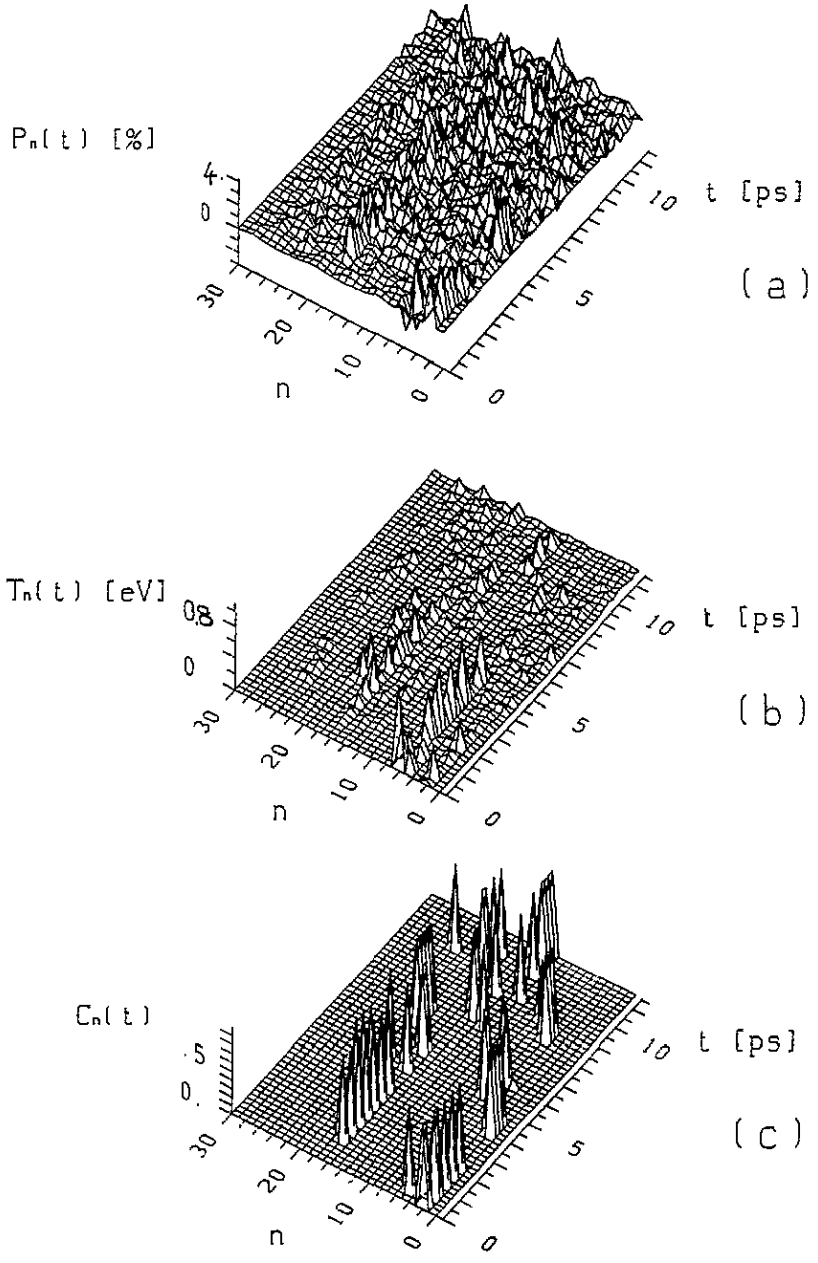

Figure 5. Like figure 4, but with an excitation energy of 4.7 eV and the initial ring size of molecule number 3 being 3.7% larger than in the ground state.

coherent state for the coordinates and a Slater determinant formed of molecular orbitals for the electrons, as was recently done for polyacetylene [38]. In this case the dynamics of the electrons can be computed explicitly. However, it is to be expected that application of this procedure would not change the results of the calculations dramatically, but would only lead to a smoother movement of the excitation from one molecule to the other, instead of the jumping obtained adiabatically.

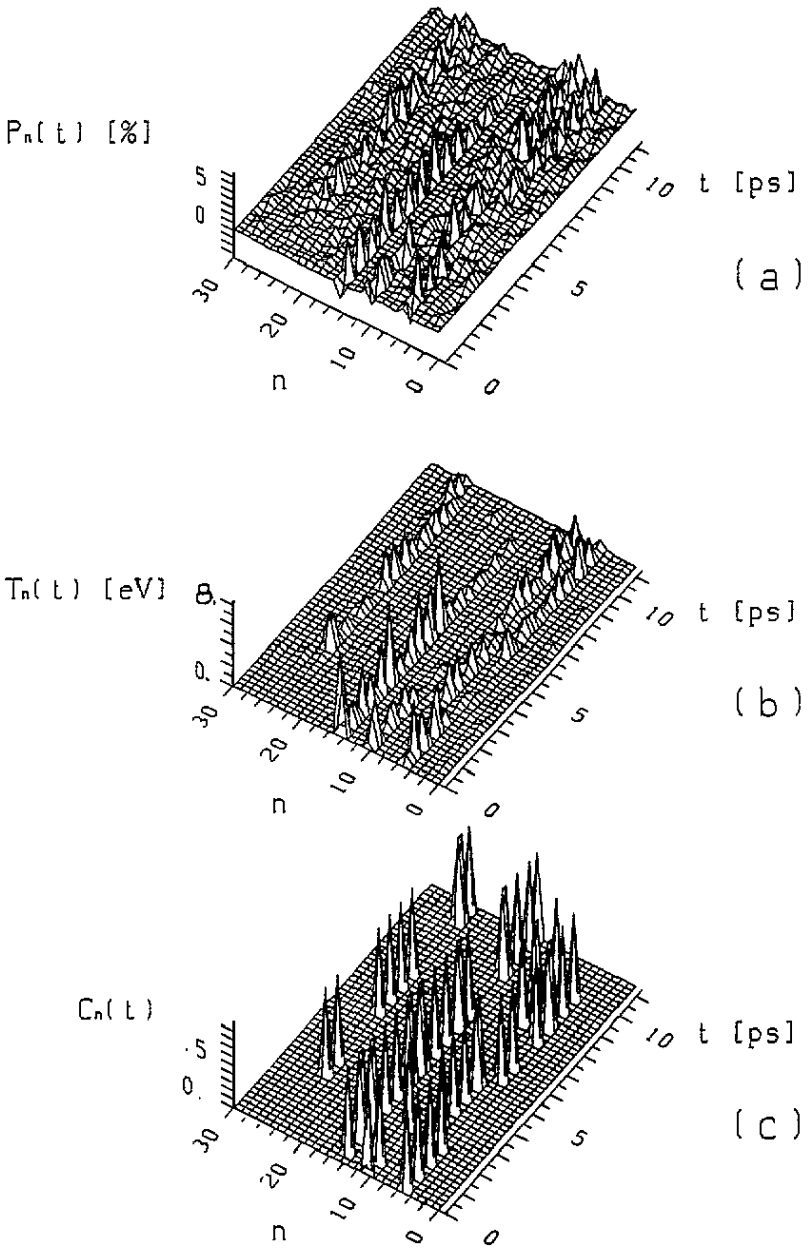

Figure 6. Like figure 4, but with an excitation energy of 9.5 eV and the initial ring size of molecule number 15 being 9.9% larger than in the ground state.

Thus the results reported indicate that in a stack of ring-shaped molecules with π-electrons, electronic excitations of one molecule do not relax immediately, but are transported in a random manner through the system. This is is exactly the behaviour required by Ladik's theory of double-strand breaks in DNA caused by irradiation ([19], [20], [22], [30]), although we do not find real solitary waves in our system. However, one still has to keep in mind that in real DNA the free movement occurring in our model is

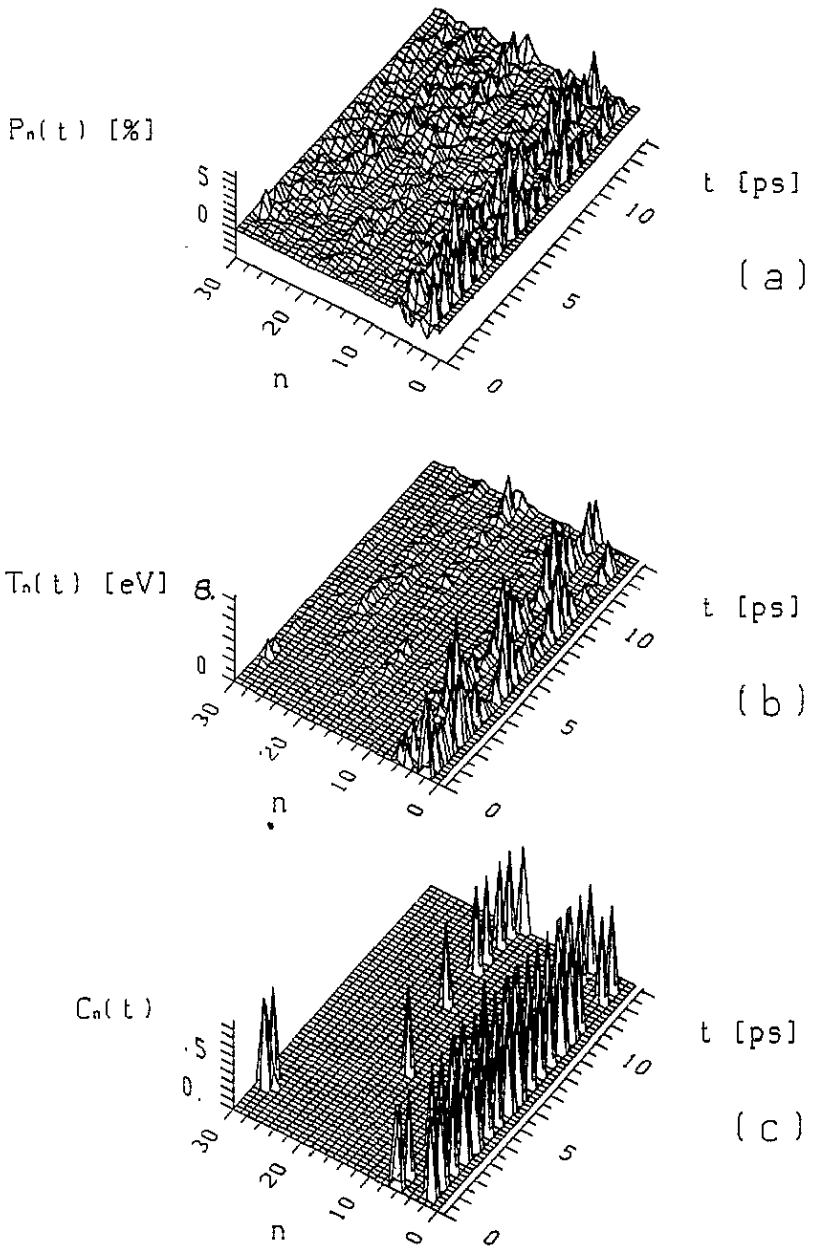

Figure 7. Like figure 4, but with an excitation energy of 9.5 eV and the initial ring size of molecule number 3 being 9.9% larger than in the ground state.

hindered first by the C–N bonds between a base and the sugar–phosphate backbone and second by the hydrogen bridges to its counterpart in the second strand. This hindering was shown to occur in the purely mechanical conformational solitary waves in DNA ([27], [28]). However, since the excited states described here interact due to the π-systems with more than just first neighbours, we expect that these hindering effects are less important for excited states than for purely conformational solitons.

Acknowledgments

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