Does the dynamics of sine-Gordon solitons predict active regions of DNA?

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Abstract

In this work we analyze the possibility that soliton dynamics in a simple nonlinear model allows functionally relevant predictions of the behaviour of DNA. This suggestion was first put forward by Salerno [Phys. Rev. A **44**, 5292 (1991)] by showing results indicating that sine-Gordon kinks were set in motion at certain regions of a DNA sequence that include promoters. We revisit that system and show that the observed behaviour has nothing to do with promoters; on the contrary, it originates from the bases at the boundary, which are not part of the studied genome. We explain this phenomenology in terms of an effective potential for the kink center. This is further extended to disprove recent claims that the dynamics of kinks [Lenholm and Hörnquist, Physica D **177**, 233 (2003)] or breathers [Bashford, J. Biol. Phys. **32**, 27 (2006)] has functional significance. We conclude that no such information can be extracted from this simple nonlinear model or its associated effective potential.

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1 Introduction

Nonlinear models supporting coherent excitations appear in many fields of science since the pioneering discoveries by Fermi, Pasta and Ulam [1] more than 50 years ago. The success of this approach in modeling complex systems has encouraged its application in other fields. That is the case of biology, where nonlinear models were widely applied in many subjects, such as in the study of the DNA molecule (see, for example, [2,3,4]). To realize the relevance of these models it should be noticed that, nowadays, the computational cost of molecular dynamics for realistic models of DNA molecules with a few tens of base pairs allows simulation times up to tens of nanoseconds at most. Nonlinear models allow the study of such a complex system with very many degrees of freedom by reducing drastically this amount up to one degree of freedom per base pair, the most relevant for the process under study. It goes without saying that the reduction of a very complicated object such as the DNA duplex to a polymer formed by base pairs, each one with just one degree of freedom (sometimes a few more) helps enormously the theoretical and computational study of this models. Nevertheless, although simplified, these models can yield important results. An example of these models is the Peyrard-Bishop model of DNA [5], which achieved an important goal when describing the denaturation process of DNA in terms of just the radial distance of the bases on each base pair [6].

Among all these approaches we focus here on the work of Englander *et al.* [7], who introduced the sine-Gordon (sG) equation as a model for DNA in 1980. The existence of sG solitons in the DNA molecule has been surrounded by controversy, as expected in a field were biology and physics do not always meet in a fruitful way [8,9]. When Englander and co-workers introduced the sG model of DNA, they based their hypothesis on experimental results that showed unexpectedly long lifetimes of open states of DNA duplexes [10]. In spite of the fact that, later, Guéron *et al.* [11] found more reasonable lifetimes, smaller by one or two orders of magnitude than the ones reported in previous works, a vast amount of literature is still based on Englander model. In this context, the aim of this work is to analyze in depth part of the literature related to the work of Englander *et al.*, providing new results that give insight into a number of important questions. Specifically, we will study the relation between the dynamics of sG solitons and the position of promoters in the genome of the bacteriophage T7. This line of work began with Salerno [12,13,14] at the beginning of the 90's and was subsequently continued in several works [15,16,17,18,19]. We stress that this is a very important issue: Indeed, if the Englander model behaviour could be connected to functionally relevant positions in the sequence, it would provide a cheap and efficient tool for genomics. Although claims in this direction have been recently presented [19], the main result of the present work is that, unfortunately, such a connection cannot be

substantiated.

The structure of the paper is as follows. In section 2 we discuss the methodology and the results of the two first papers about this issue [12,13] in terms of the effective potential introduced by Salerno in collaboration with Kivshar in [14]. In section 3 we describe the main features of the promoters of the T7 genome, and analyze the simulation results of the work of Lennholm and Hörnquist [16] in terms of the effective potential. In section 4 we discuss recent work about breathers in the sG model [19]. Finally, section 5 concludes the paper by summarizing our main results and their implications.

2 Early work on $T7$: A_1, A_0 and A_3 promoters

More than a quarter of a century ago, Englander and coworkers [7] introduced solitonic excitations into the DNA world as an initial step towards understanding the stability of open segments of DNA molecules [10]. They suggested the well-known sG model, that describes the dynamics of a line of pendula in a vertical gravitational field with torsional spring coupling between units, as an effective description of DNA molecules. In this way, the double-helix is approximated by two parallel rods on which pendula (base pairs) are attached, and bonding to the opposite base is represented by a "gravitational" potential of each pendulum. Calling ϕ_i the twist angle of the i-th base, this model has static soliton (kink) solutions given by

$$\phi_i = 4 \arctan\left(\mathrm{e}^{ai}\right), \tag{1}$$

valid for $a \ll 1$, where the continuum approximation applies. In equation (1), a is a dimensionless parameter representing the parameters of the model, and acts as an effective discretization parameter of the continuum sG problem. In spite of such a great oversimplification of the real problem, the model contained the main feature of breaking a bond around $\phi = 0$. In addition to this, the results were consistent with available data [10] although Englander *et al.* were aware of the lack of evidences of solitonic excitations.

Salerno, in his pioneering and interesting work [12], tried to find a relation between relevant sites in the $T7$ genome and the dynamics of sG kinks moving along the inhomogenous DNA sequence under study. The main difference with respect to previous works was the introduction of the inhomogeneity of the sequence in the model. To do so, he took the static kink solution (1), with center at n_0, and used it as initial condition of the equations of motion of the discrete, *inhomogeneous* sG (or Englander) model,

$$\ddot{\phi}_i = \phi_{i+1} - 2\phi_i + \phi_{i-1} - q_i \sin\phi_i, \tag{2}$$

q_i being the parameter that carries all the information of the sequence under study. It is defined as $q_i = \beta\lambda_i/K$, where K is the torsional spring constant between consecutive bases, β is the energy of a hydrogen bond and λ_i is the number of hydrogen bonds in a base pair, which is $\lambda_i = 2$ for AT base pairs and $\lambda_i = 3$ for CG base pairs. Considered as a discrete version of the continuum sG equation, the effective discretization of the lattice used in [12] was $a = \bar{q}^{\,1/2}$, where $\bar{q} = \frac{1}{N}\sum_{i=1}^{N} q_i$ (N being the number of bases of the sequence). This value is around $a \simeq 0.07$, which is small enough to avoid spurious discretization effects when numerically integrating Eq. (2). In fact, taking Eq. (1) as an *Ansatz* in Eq. (2) was a good choice, as the kink is a very robust object even in inhomogeneous sequences and its center can be well defined by interpolating the position where $\phi = \pi$ [17,18].

Once the model was defined, Salerno built a sequence $\{q_i\}$ to introduce it in (2). He was interested in the genomic sequence of the $T7$ A_1 promoter but, instead of using the original DNA sequence, he built a "synthetic" one from the original. We will review all the details of this process as this will be the key to understand the results of [12]. He took a sequence S of 168 bases containing the so-called A_1 promoter (further details on $T7$ promoters will be given in the next section) which corresponds to base pairs (BP) from 378 to 545 of the actual $T7$ genomic sequence, and built a longer sequence of 1000 bases, that we will call S', to prevent the influence of boundary conditions on the dynamics of kinks:

$$S' = S(1,5) + 8S(1,50) + S(1,168) + 15S(141,168) + S(162,168). \qquad (3)$$

In this way, the 168 bases sequence S would remain in the center of the new sequence S', with the transcription start site located in BP 526 and the promoter sequence going from BP 509 to BP 531, far from the limits of the lattice. Therefore, reflective boundary conditions could be safely used in the numerical simulations. We will return to this issue when discussing the results.

As was known that the RNA polymerase could bind to DNA in the region of S going from BP 51 to BP 140 (going from BP 455 to BP 545 in S'), the expectation was that this region should be dynamically active. Hence, in [12] several integrations of Eq. (2) were carried out with the initial position of the static kink in a variety of sites inside the promoter region and the behaviour of the kinks was studied as a function of their starting position. The results were the following: For initial positions in S' from BP 415 to BP 505 the kink remained static or with small oscillations around the starting point. For BP 510, the kink acquired a velocity $v = 0.18$ towards the left, was reflected without loss of energy at the left boundary and reflected again at the promoter region with velocity $v = 0.18$. This behaviour was enhanced when the initial position was increased from BP 510 to BP 535, where the kink also reached the maximum velocity $v = 0.3$. Beyond this point this dynamical behaviour was

drastically reduced. For BP 540 the kink acquired a small velocity ($v \simeq 0.08$) towards the right, and for BP 555 the kink simply remained at rest. The dynamics of a kink with initial velocity $v = 0.3$ towards the left was also studied, starting from BP 900; it was found that the soliton was accelerated when it traveled from right to left through the central region, then reflected at the left end of the sequence and decelerated when traveled in the opposite direction. It was concluded in [12] that these results showed the existence of a dynamically "active" region going from BP 510 to BP 540 inside the $T7$ A_1 promoter that could explain the functioning of DNA promoters as energetic activators of the RNA polymerase transport process.

In a subsequent paper, Salerno and Kivshar [14] introduced the effective potential in order to explain the behaviour of these objects when moving in a inhomogenous sequence. The idea is that kink robustness allows to approximate their dynamics, even though they are extended objects, as if they were point-like particules moving along a one-dimensional potential, given by

$$V_{\text{eff}}(n) = \frac{\sum_m (\bar{q} + q_m)\text{sech}^2(a(m-n))}{2\sum_m \text{sech}^2(a(m-n))}. \tag{4}$$

Recently this approach has been shown to give good results for Fibonacci [15] and DNA sequences other than the $T7$ one [17,18]. By "good results" we mean that the dynamics of the kink in Eq. (2) and that of the particle in the effective potential (4) can by aligned, in the sense that trajectories are semiquantitatively similar, equilibrium points for the kink correspond to minima of the potential, and so on. This was also the case with the effective potential introduced in [14]: This paper reported the agreement of the direction of motion of the kinks according to the effective potential curve corresponding to the sequence S', plotted from BP 425 to BP 605 (see Fig. 1). As can be seen from the figure, there is indeed a good correspondence between the effective potential and the simulation results summarized above.

However, a more detailed analysis shows that this correspondence is not enough to establish a relation between DNA promoters and dynamically "active" regions. In Fig. 2a it is plotted the effective potential $V_{\text{eff}}(n)$ (taking $V_{\text{eff}}(500)$ as the origin of energies) for sequence S' and for the original $T7$ genome sequence. From this figure we immediately observe, on the one hand, that the positions of the peaks and the wells of the effective potential of sequence S' explain very well the above kink dynamics results reported in [12] in terms of a point-like particle; and, on the other hand, that the effective potential of the original $T7$ genome *far from the* A_1 *promoter* is very different from the one of the S' sequence, and hence the dynamics of kinks must be different, too. Fig. 2b shows the dynamics of two kinks on the two sequences, S' and the original $T7$ sequence. It is clear that the dynamics behaviour of both sequences is largely different: for instance, in the true potential BP 510 should

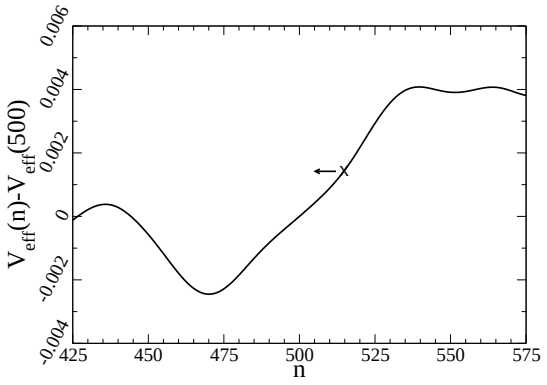

Fig. 1. Effective potential for $a = 0.07$ of sequence S' from BP 425 to BP 605. The only difference with the one represented in [14] is that, in the latter, an additional average of the potential over a distance equal to $\bar{q}^{\,-1/2}$ was made.

not be regarded as an active site whereas BP 680 should be regarded so. The comparison of the trajectories with those obtained from the effective potential confirms the validity of this potential to describe the dynamics of kinks (allowing for a difference in time scales, as in the point-like particle description time units are arbitrary). This means that the effective potential is a correct description for both the real sequence and S', and therefore the differences between both of them are not an artifact of this approximation. These differences between the two potentials come from the periodic sequences introduced in (3), $8S(1, 50)$ and $15S(141, 168)$, adjacent to the 168 nucleotide S sequence. The AT/CG content in the periodic sequences has an average value around which the effective potential of these sites oscillates. As further evidence of the influence of the ends of the sequence, in Fig. 3 we show the effective potential of sequences S', S'_1 and S'_2, with $S'_1 = 405\,A + S(1, 168) + 427\,A$ and $S'_2 = 405\,C + S(1, 168) + 427\,C$, where $N\,A$ ($N\,C$) means N consecutive sites with nucleotide A (C). The effective potentials for kinks moving along S'_1 and S'_2 will lead to a very different dynamics from that described in [12] and reported here, although they all have the same central sequence of 168 nucleotides.

In [13] the same methodology developed in [12] was used to analyze another two $T7$ promoters, namely A_0 (also called D) and A_3, and similar results were obtained (see Table 1). Figs. 4a and 4b show the effective potential of the synthetic sequences built by Salerno from the genomic 168 nucleotide sequences and the effective potentials of the real T7 sequences around the promoters. Again, the effective potentials of the synthetic sequences describe the results of the dynamics summarized in Table 1, but differ from the effective potentials of the real genomic sequences, yielding different dynamics. For instance, according to Fig. 4a, a kink starting from BP 245 in the real genomic sequence around A_0 promoter would reach the right end of the sequence, instead of oscil-

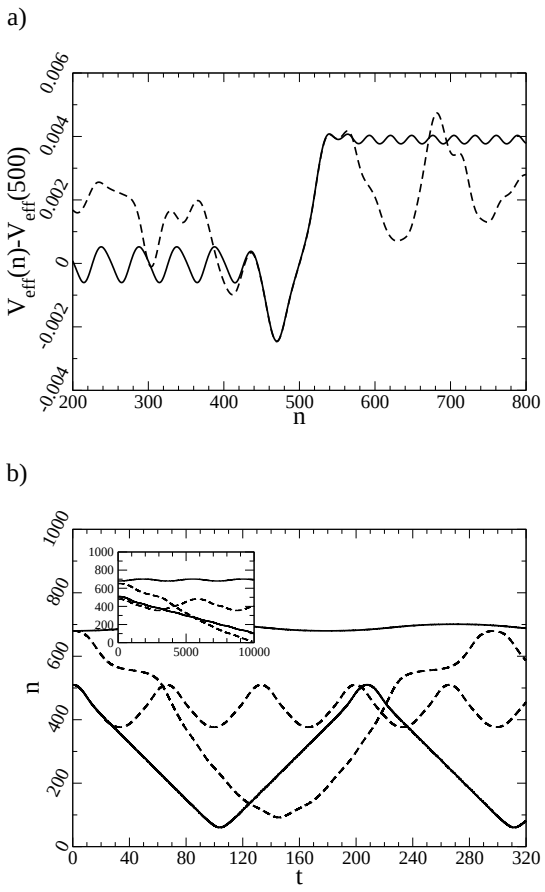

Fig. 2. (a) Effective potential for $a = 0.07$ around the $T7$ A_1 promoter for the synthetic sequence S' (solid line) and for the original genome sequence (dashed line). The potential of the original sequence has been shifted in the horizontal and vertical axis to make it coincide with the one of the 168 bases sequence S in S'. (b) Dynamics of the center of two kinks (calculated by interpolating the position where $\phi = \pi$), moving along S' sequence (solid lines) and the real $T7$ genome sequence (dashed lines), starting from BP 510 and BP 680. Inset: point-like particle dynamics starting from the same sites and moving according to the corresponding effective potentials of (a). Although the dynamics is scaled in time with respect to the kink dynamics, the trajectories of each pair particle/kink are the same.

lating around the initial starting position, as it would do in the corresponding S' sequence.

We note that in [13] it was argued that, as the initial static soliton was always well inside the original 168 base sequences, then the flanking regions used to prolog the chain played no role in the dynamical effects described. However, we have just shown how important they are when the kink moves towards them. Therefore, we are forced to conclude that the results in [12,13] are highly dependent on the construction of sequences S', and that when the original $T7$ genome sequence is used instead then the promoter regions cannot be considered "active" or "special" regions anymore. As we have seen, other

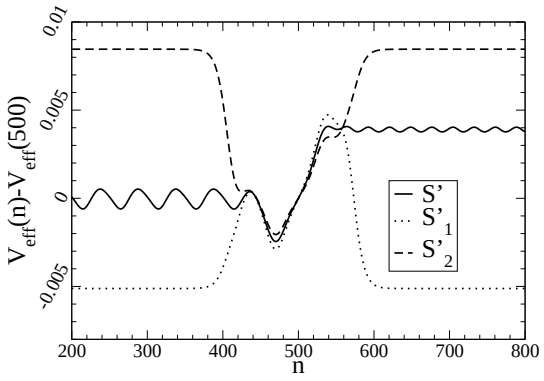

Fig. 3. Relevance of the end parts of the sequence: Effective potential for the synthetic sequences S', S'_1 and S'_2 (see text for definitions).

Promoter	**BP region**	**Response**
A_1	From 510 to 535	Leftward propagation, strongest at 535.
	540	Small velocity towards the right.
A_0 (or D)	From 530 to 540	Leftward propagation, strongest at 540.
	From 543 to 555	Rightward propagation, strongest at 543.
A_3	From 435 to 460	Rightward propagation.

Table 1
Summary of the dynamical results for kinks moving in the synthetic sequences S' obtained from A_1, A_0 (also called D) and A_3 promoters in [13].

regions close to, but different from, the promoters may be even more "active" in the sense of inducing kink motion; conversely, some active regions in the synthetic sequence lose this character in the real genome.

3 Subsequent developments: full $T7$ genome

Following the interesting proposal of Salerno, namely the putative relation between $T7$ promoters and the dynamics of solitons moving along inhomogeneous genomic sequences, further research intended to shed further light on this question [16]. The main contribution of this sequel is that the sequences used were real genomic sequences and, in addition, that the whole $T7$ genome was studied.

In the research reported in [16], Lennholm and Hörnquist measured the maximum distance (in either direction) reached by initially static kinks starting from each of the sites of the whole sequence of the $T7$ genome. They also took

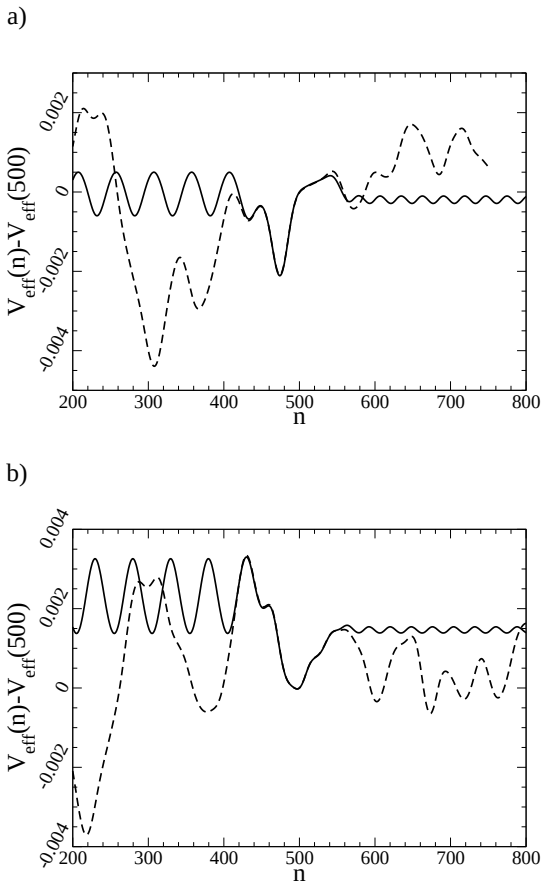

Fig. 4. (a) Efective potentials for $a = 0.07$ of the synthetic sequence S' (solid line) and for the original genome sequence (dashed line) around $T7$ A_0 (also called D) promoter. The sequence used in [13] corresponds to the transcription strand (this promoter activates transcription leftwards, and therefore it uses the complementary strand of the sequence usually showed [20,21]) in the transcription order. Therefore, the original sequence has been written in reverse order in order to obtain its potential, and then shifted in the horizontal and vertical axis to make it coincide with the potential of the S sequence in the synthetic S' sequence. (b) Efective potentials for $a = 0.07$ of the synthetic sequence S' (solid line) and for the original genome sequence (dashed line) around $T7$ A_3 promoter. The potential of the original $T7$ sequence has been shifted in order to make it coincide with the potential of the S sequence in the synthetic S' sequence.

the 24 promoters of the $T7$ genome (except the first and the last ones to avoid boundary effects), studied the results obtained for positions going from -4 to -1 of each promoter and compared these results with the results of the whole genome. The aim of this analysis was to find whether the RNA polymerase melting region (the one going from -4 to -1 in each promoter) acts as a dynamically "active" region as proposed by Salerno, or behaves in the same way as the rest of the nucleotides of the genome. In this respect, they did not found relevant differences (see Fig. 1 of [16]). However, for every promoter they investigated the activity of the first n base pairs which are transcribed by RNA

polymerase and found that, for $n = 20$, the studied regions are more active than average with a significance of more than five standard deviations (see Fig. 2 of [16]). They did not give any biological interpretation of that results but, in their conclusions, they suggested that a more quantitative relation between kink motion and the effective potential should be established.

As already mentioned, this paper as well as our previous work [15,17,18] has proven the agreement between kink dynamics and effective potential. Therefore, we can now study the whole $T7$ genome in terms of this tool. To this end, we will review some of the properties of the $T7$ promoters in order to set a methodology in the study of the effective potential in these regions. The $T7$ phage genome is one of the most studied genomes since the whole genome sequence was found in 1983 [20], and few changes in the sequence have been reported since then [21]. The reproductive cycle of the $T7$ phage is closely linked to the promoter and gene distribution in the genome. When the $T7$ RNA is injected inside a bacteria, like *E. coli*, the bacterial RNA polymerase starts to produce mRNAs induced by three major promoters from the early region (or class I region) A_1, A_2 and A_3. A fourth major *E. coli* promoter, A_0 (also called D), that would direct transcription leftward, and several minor *E. coli* promoters function in vitro but have no known in vivo function. Once the $T7$ phage has its own transcription machinery, late mRNAs are produced by 15 promoters for $T7$ RNA polymerase distributed across the right-most 85% of the DNA (divided in class II and class III region). There are also two $T7$ promoters associated with possible origins of replication at the left and right ends of $T7$ DNA. The 23 base-pair consensus sequence for $T7$ promoters stretches from -17 to +6, where +1 is the transcription start site. This means that the nucleotides of the promoters are highly correlated in these sites (although sometimes they are not strictly the same), but not in the rest of the sequence (we will come back to consensus sequences below).

We can now go back to our main aim: We want to find out whether or not there is some kind of pattern in the effective potential, or a set of properties to be applied to all the promoters in the $T7$ genome that allow their identification among the rest of the genome. To this end, we must keep in mind that the effective potential on each site [see Eq. (4)] is just a weighted average of the sequence around the site, with weight function $\mathrm{sech}^2(an)$. We can obtain an estimation of the resolution of the effective potential reading frame by noticing that an error of about 10% in the effective potential is introduced when truncating the sum in the weighted average (4) in $\pm\Delta n = 1.5a^{-1}$ around each n. If we consider that, for further sites, the contribution of the q_m to the weighted average is negligible, then the number of sites averaged when computing the effective potential on each site goes as $\Delta n \simeq 3a^{-1}$. This means that, for $a \simeq 0.07$ (which is the approximate value of the discretization as explained in section 2), Δn is about 40, a much lower resolution than the one needed to recognize the 23 base-pair consensus sequence in the effective

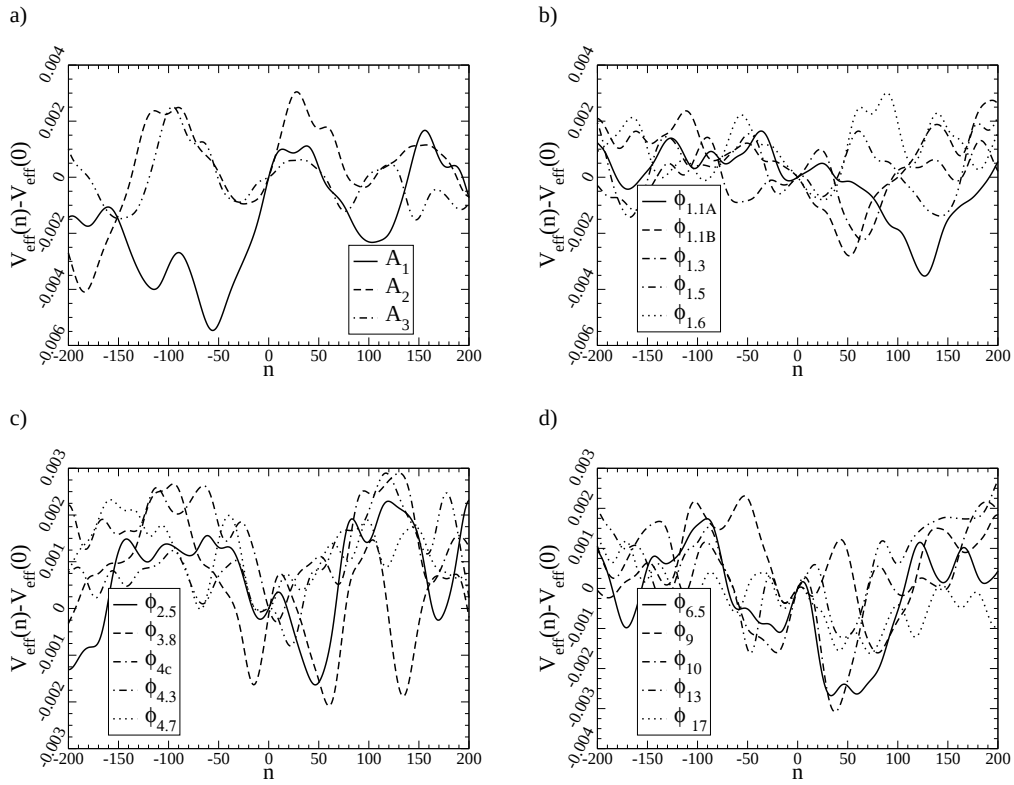

Fig. 5. Effective potentials for $a = 0.07$ around the transcription start site of: (a) Early A_1, A_2 and A_3 E. coli promoters; (b) Late $\phi_{1.1A}$, $\phi_{1.1B}$, $\phi_{1.3}$, $\phi_{1.5}$ and $\phi_{1.6}$ $T7$ promoters; (c) Late $\phi_{2.5}$, $\phi_{3.8}$, ϕ_{4c}, $\phi_{4.3}$ and $\phi_{4.7}$ $T7$ promoters; (d) Late $\phi_{6.5}$, ϕ_{9}, ϕ_{10}, ϕ_{13} and ϕ_{17} $T7$ promoters. Origins are referred to the transcription start site in all cases.

potential. Therefore, we conclude that the kink is too wide to allow us to check that the same curve describes the effective potential of different promoters, as was suggested in [12,13,16]. On the other hand, we can increase the resolution of the effective potential by increasing the discretization a until reaching $\Delta n = 1$. We could find then the consensus sequence repeated in the effective potential around each promoter, but that would not give more information than the consensus sequence itself, and the effective potential would not be useful from a genomic point of view.

To go beyond the previous theoretical discussion, we have computed the effective potential for most of the $T7$ promoters for $a = 0.07$. In Fig. 5 we show the effective potential of the three major *E. coli* RNA polymerase promoters (early promoters) and the T7 RNA polymerase promoters (late promoters) of $T7$ for $a = 0.07$. Clearly there is no "consensus effective potential" that appears in all (neither in most) of the promoters. If we were looking for more subtle properties that might enclose all the 18 promoters or each subset of early and late promoters, then we would be led to consider as promoters other regions of the $T7$ genome which are not. As an example, the effective poten-

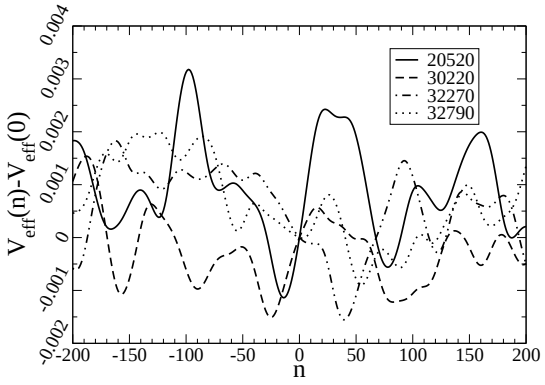

Fig. 6. Effective potential for $a = 0.07$ in different sites of the sequence, which may look like the effective potential of promoters in Fig. 5 but which are not. The origin of each sequence corresponds to the number in the legend box.

tials around some other regions that are not promoters are plotted in Fig. 6, and it is shown how alike they are to the ones of Fig. 5. Hence, we believe that the effective potential of kinks, and therefore the dynamics of kinks in the inhomogenous sG model cannot explain the initiation in the promoters of the transcription process in the $T7$ phage and, probably, in any other organism.

We now turn to the work in [16] in order to understand the difference with the conclusions reported there. The research in [16] is certainly interesting because, as we already said, it is the first time that the whole genomic sequence of the $T7$ phage is taken into account. However, we believe that their methodology is not appropriate for the case under study, as the statistical analysis of kink dynamics does not give conclusive results. For instance, a graph with the furthest position reached in the sequence in terms of the initial position from which the kink started to move would have yielded different results from the ones reported in [12,13] and the work would have been more conclusive. In addition, we note that the direction of motion of the kinks was not recorded and therefore it cannot be assessed whether or not the "activity" of those regions agrees with the transcription direction. We therefore conclude that an individual study of each promoter is needed if functionally relevant places are to be found. This individual study is what we have presented here and we believe that the conclusion is clear: The effective potential shows no signature of the promoters. Having verified this, in the next section we show that, if a detailed study of promoters is done, it must be over all the promoters of the phage in order to be conclusive.

4 sG breathers

In this last section, we consider yet another recent approach to sG soliton dynamics that followed the steps of [12,13,14] but using breathers instead of kinks [19]. In this case, the author studied RNA polymerase recognition of specific binding sites by comparing breathers to localised deformations of the DNA duplex when the RNA polymerase slides on its major groove. To this end he constructed a potential for sG breathers following the steps of [14], but using as *Ansatz* a discretized breather, given by

$$\phi_{\mathrm{br},n}(t) = 4\tan^{-1}\left(\tan\mu\frac{\sin(t\ \bar{q}^{\,1/2}\cos\mu)}{\cosh(n\ \bar{q}^{\,1/2}\sin\mu)}\right), \tag{5}$$

where μ is related to the intrinsic frecuency of the breather. The potential obtained in [19] is the following:

$$V_{\mathrm{br}}(n) = 4\tan^2\mu\sum_m \frac{(\bar{q}+q_m)\cosh(a(m-n))}{\left(\tan^2\mu+\cosh^2(a(m-n))\right)^{3/2}}, \tag{6}$$

with $a = \bar{q}^{\,1/2}\sin\mu \simeq 0.04$. The main difference between this potential and the one obtained in [14] is that breathers defined by (5) are not static solutions of the sG model. This means, on the one hand, that the kinetic term of the sG Hamiltonian (that we do not write here) has two extra terms when deriving $\phi_{\mathrm{br},n-n_0(t)}$ with respect to time and squaring it, and that the potential term obtained depends explicitly on time. These problems may be solved by moving one of the extra terms from the kinetic to the potential term, and then integrating in time over a period. Another important difference with [14] is that kinks are very robust objects that behave very well in the discrete sG model, even for inhomogeneous sequences, and that is why they can be expressed in terms of its center. Breathers, however, are very unstable in the homogeneous, discrete sG model, and it is to be expected that they are even more so on inhomogeneous sequences. Therefore, we do not think that the potential for breathers may describe accurately and/or for long times the dynamics of an initially static breather. The construction of the sG potential for breathers is, therefore, not as straightforward as the one for kinks in [14], and this must be taken into account when analyzing the results.

After the breather potential (6) was constructed in [19], it was used to analyze the early region of the $T7$ genome and a particular region of the $T5$ phage. It was suggested, among other things, that there is a correlation between deep wells of (6) and promoters in the early region and class III $T7$ promoters. Another relation between deep wells and transcription terminators was also suggested. We can now apply the results obtained in section 3 to the claims

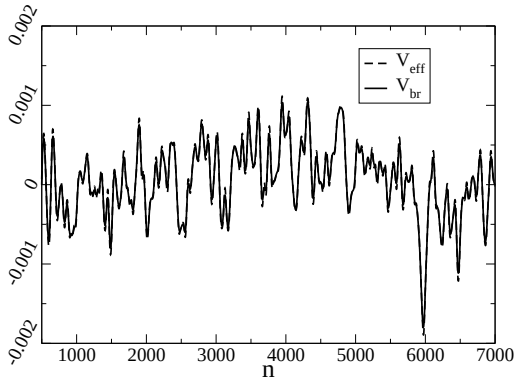

Fig. 7. Potential $V_{\rm br}$ (6) for breathers (solid line) and $V_{\rm eff}$ (4) for kinks (dashed line) for the $T7$ genome region going from BP 500 to BP 7000 for $a = 0.04$ and $\mu = \pi/6$ (which corresponds to the values used in the figures of [19]). The scale of $V_{\rm br}$ has been divided by 50 in order to make it fit with the scale of $V_{\rm eff}$. No vertical shifting was made in any potential. This region of the genome contains seven promoters.

in [19] by noticing how alike the weight functions of (4) and (6) they are for $\tan\mu < 1$ (which is the case, according to [19]). Therefore, the structure of peaks and wells is very similar in both cases, as shown in Fig. 7, and we can thus extend the conclusions of section 3: Even if the potential for sG breathers works in a similar way as the effective potential for sG kinks, it is not enough to explain the transcription process of RNA polymerase. For instance, as shown in [19], there are deep wells in the potential for sG breathers near some of the promoters of the $T7$ genome. However, there are other promoters (class II) which are not near any deep well, and also deep wells which are not near promoters (like the ones found in [19] near terminators). When loosing the constraints in order to take into account not so deep wells which are near promoters, then many other wells far from promoters should be considered, too. We therefore conclude that there is no special characteristic in the potential for breathers that allow the identification of promoters from the rest of the genome, by simply looking at the effective potential.

5 Conclusions

The Englander model was introduced in [7] to explain long life times on open states of DNA duplexes [10] by means of the well known nonlinear sG model. Subsequently, research on the sG model led to suggestions of a relation between functionally relevant positions in the sequence with dynamical properties of sG solitons. In section 2 we showed that the results of kink dynamics moving along inhomogenous sequences developed in [12,13] depend highly on the sequence under study. In order to achieve this we used the effective potential

for sG kinks moving on inhomogeneous sequences, introduced in [14]. Applied to the sequences used in [12,13] and to the corresponding real genomic sequences of the $T7$ phage, we observed important differences between both potentials. Differences came from the end parts of the analyzed sequences, which were a priori assumed not to have any role. With these findings and taking into account the good results already obtained for the particle-like approximation of sG kinks moving along inhomogeneous sequences [15,17,18], we concluded that early promoter regions of the $T7$ genome cannot be considered dinamically "active". In section 3, addressing the question posed in [16], we searched for patterns that could differentiate the dynamics of kinks starting from $T7$ promoters from kinks starting from the rest of the genomic sequence. Again, we used the effective potential, this time applied to the whole genomic sequence of the $T7$ phage. Comparing the curves obtained for the 18 major promoters of the phage among them and also with other non-promoter regions led us to think that there was no special properties of the effective potential around promoter regions, and therefore that the dynamics of kinks moving from these regions was the same as in other genomic regions. Finally, in section 4 we applied the same arguments and also reviewed the problems of the potential for breathers in order to demonstrate that the potential for sG breathers obtained in [19] can not be used to differentiate promoter regions in the genomic sequence. From all this evidence, we can confidently claim that neither the sG model nor its description in terms of the effective potential give hints about functionally relevant sites of DNA sequences. We stress that this claim is about the sG model and the dynamics of its solitons. Statistical mechanics approaches are also being studied with some success [25,22,23,24] but that is a completely different approach.

It is important to extend this discussion to include its biological implications. The relation of deep wells and functioning sites of DNA can now be discussed in terms of properties of bacterial promoters [26,27]. Bacterial RNA polymerase is a multisubunit complex. A detachable subunit, called σ factor, is responsible for reading the promoters, which are the signals enconded in the DNA that tell it where to begin transcribing. Most bacteria contain multiple σ factors that enable the recognition of different sets of promoters. A comparison of many different bacterial promoters reveals that they are heterogeneous in the DNA sequence. However, they all contain related sequences that reflect on mechanical and electrostatic properties of the DNA double helix that are recognized by the σ factor. These common features are often summarized in the form of a consensus sequence, which serves as a summary or "average" of a large number of individual nucleotide sequences. The precise sequence determines the strength (or number of initiation events per unit time) of each promoter. However, although the σ factor is needed in the transcription initiation, other elements can bind to RNA polymerase to regulate the transcription of specific promoters, like the α subunits. Another important group of proteins that recognizes and binds to promoters are transcription factors. These pro-

teins act as regulatory elements that control transcription initiation and bind to specific sequences. This summary of regulatory elements of transcription initiation in procaryotes reveals the intrinsic complexity of the sequences of promoters. In the case of eukaryotic regulation the complexity increases too much to try to summarize it in this paragraph, and we will just refer to the counter-intuitive fact that specific CG-rich promoters that are found in yeast [28]. Therefore, we conclude that, although deep wells in the potential for sG kinks or breathers are correlated with AT-rich regions, they are not enough to recognize such complex structures as promoters, and it is only natural that the dynamics of these simple excitations cannot capture the mechanisms of promoter function.

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