Conclusions

The work presented in this thesis is devoted to the development of a DNA model which could describe some of the dynamical features involved in the process of transcription initiation. Our aim was the description of a complex biological process by a simple model, avoiding trivial simplifications which may lead to a complete loss of connections with real phenomena. It has thus been important to proceed carefully: we presented our results as to emphasize all the steps which lead us to the construction of the model.

The *twist-opening* model reproduces the main features of the local geometrical structure of DNA, described in a mesoscopic scheme where nucleotides represent the fundamental units. With respect to previous studies we include in the description, beside base pair opening, helix torsion, which is the degree of freedom most directly coupled with the opening itself.

The model Lagrangian is obtained by considering first the hydrogen bonds linking the two bases in each pair, and then modeling the coupling between bases on the same strand by means of elastic rods of finite length. The helical geometry is obtained by imposing a fixed distance between the base pairs planes, so that rods have to be inclined at equilibrium. Furthermore, to favor an uniform clockwise (or counterclockwise) rotation of the inclined rods we also add a three-body curvature term in the angles.

The resulting Lagrangian leads to a correct equilibrium configuration and provides a coupling between radii and angles which has the desired properties. Nevertheless, we have observed that we must add a direct stacking interaction between neighboring base pairs, which is due in real DNA to an overlap between π electrons. We have therefore added a new potential term which can account for the direct stacking interaction, obtaining the final, improved form of our Lagrangian. We have considered both the original and the improved models in performing all the numerical and analytical calculations. The improved model behaves much better in all cases, leading to a satisfactory agreement with known DNA properties.

In simulated canonical conditions, the model is able to reproduce the denaturation transition of DNA, with a reasonable accuracy, that could be improved with a better choice of some of the model parameters. Two of the parameters remain in fact to be chosen, due to the lack of experimentally available data.

The model also reproduces some of the dynamical properties of DNA in constant temperature conditions, *i.e.* it shows the formation, through thermal energy localization, of localized oscillating excitations with a frequency which corresponds to the one measured experimentally. The helical twist turns out to strongly constrain the denaturation transition: we show that denaturation needs, as it happens for real DNA, a complete untwist of the helix, in order to allow the two strands to uncoil and separate. Furthermore, we have showed the presence of a dependence of the sharpness of the transition on the single strand rigidity.

Moreover, the model is simple enough to allow an analytical approach. Analytical solutions, which correspond to the thermally generated oscillating distortions, have been found by the expansion in multiple scales we have developed for vectorial lattices. The operatorial formalism we have presented allows in fact to calculate approximate breathers of the model. These breathers are characterized by an oscillating opening of base pairs coupled with an untwist of the helix. Their shape is a result of the geometrical constraints and confirms that the helical geometry plays an important role in DNA opening.

The final aim of the model presented herein was a deeper understanding of the possible mechanisms which allow biological processes as long range activation and bubble formation in the initiation phase of transcription.

Let us list some of the main research directions that can be followed by means of the *twist-opening* model.

1. For bubble formation, one possible mechanism which has been suggested is related to the fact that RNA-polymerase bends the promoter, inducing DNA structural changes that can be simulated by changes in the model constants. The resulting inhomogeneity could act as a trap for small breather distortions. It is now possible to simulate this mechanism in the context of a realistic description of the DNA structure. The existence of analytical solutions allows to control the shape of the distortion and dynamical properties in order to make systematic studies. Furthermore, it can probably lead to a deeper understanding of the resulting process through an analytical reconstruction of its features.

2. To draw some conclusions on the long range activation mechanism will be instead a more difficult task. We have shown that moving distortions can travel along the DNA chain. They could have some effects on protein binding sites or on the interactions between DNA and proteins. Anyway a better description of these interactions must be introduced if we want to examine the possible effects of localized moving distortions. Modeling DNA-protein interaction is very hard at present, but perhaps it may be possible by focusing on some specific cases. It will be possible moreover that secondary distortions could be represented in terms of helical twist distortions or in terms of changes in the parameters of the model.

3. The introduction of local inhomogeneities could then be extended to the whole chain, reproducing the differences between AT and GC base pairs, in order to investigate the properties arising from the specific DNA sequence. The effects on breather motion of special (real) DNA regions as promoters or enhancers could be investigated. More generally, we can study breather propagation in disordered media, obtained by introducing inhomogeneities with different statistical correlations.

4. Further studies could be done on the basis of the *twist opening* model by referring to properties arising directly from its geometry. One of its interesting properties is for instance the possibility of a transition from left-handed to right-handed chain, which will mimic transitions to Z-DNA. Z-DNA is known to have important properties in transcription activation/repression mechanisms, which are actually investigated in current biological research, so that an analysis of their interaction with breathers, or a description of the dynamical properties of the interface between the two configurations, could represent an interesting topic.

5. Finally, from the point of view of statistical mechanics, the twist opening model is an interesting example of a one-dimensional model that shows thermodynamic properties (such as the existence of a denaturation transition) which are governed by boundary conditions. This will deserve further investigations.

It may seem presumptuous to attempt to investigate one of the fundamental processes of life, DNA transcription, from a purely physical approach. Certainly we cannot claim that we have such an ambitious goal. We however believe that, whatever its complexity, biology could benefit from a physical approach that tries to determine some features that are at the essence of the processes and we hope that the model we have presented in this work is one step in this direction.