Analysing DNA structural parameters using a mesoscopic model

Tauanne D Amarante and Gerald Weber

Universidade Federal de Minas Gerais - Instituto de Ciências Exatas - Departamento de Física, Av. Antônio Carlos, 6627, Belo Horizonte, Minas Gerais CEP 31270-901, Brazil, Tel 55-31-3409-5633 Fax 55-31-3409-5600

E-mail: tauamarante@gmail.com

Abstract. The Peyrard-Bishop model is a mesoscopic approximation to model DNA and RNA molecules. Several variants of this model exists, from 3D Hamiltonians, including torsional angles, to simpler 2D versions. Currently, we are able to parametrize the 2D variants of the model which allows us to extract important information about the molecule. For example, with this technique we were able recently to obtain the hydrogen bonds of RNA from melting temperatures, which previously were obtainable only from NMR measurements. Here, we take the 3D torsional Hamiltonian and set the angles to zero. Curiously, in doing this we do not recover the traditional 2D Hamiltonians. Instead, we obtain a different 2D Hamiltonian which now includes a base pair step distance, commonly known as rise. A detailed knowledge of the rise distance is important as it determines the overall length of the DNA molecule. This 2D Hamiltonian provides us with the exciting prospect of obtaining DNA structural parameters from melting temperatures. Our results of the rise distance at low salt concentration are in good qualitative agreement with those from several published x-ray measurements. We also found an important dependence of the rise distance with salt concentration. In contrast to our previous calculations, the elastic constants now show little dependence with salt concentrations which appears to be closer to what is seen experimentally in DNA flexibility experiments.

1. Introduction

Many simplified models were proposed to describe the denaturation of DNA. A specific class of such models, called mesoscopic models have the advantage that their parameters have straightforward physical interpretation and can be compared directly with experimental data. One of these models, the Peyrard-Bishop (PB) model [1], is a simple mechanical model for DNA that associates two degrees of freedom for each base pair confining the molecule to a plane. These two degrees of freedom are further reduced to a single variable by linking the strand separation to the stacking distance [1]. This results into a powerful and computationally efficient method which allows us to extract relevant DNA parameters, such as hydrogen bonds, from experimental melting temperatures [2, 3]. Therefore, it is tempting to apply such methods to 3D helicoidal forms of the Peyrard-Bishop Hamiltonians [4, 5] to obtain further structural information about DNA. However, the added degrees of freedom represented by 3D Hamiltonians are not yet tractable by current melting temperature fitting methods. Nevertheless, one possibility is to adapt the 3D torsional models to a simpler 2D format and use them with the existing methods to retrieve DNA parameters.
Here we use the angular forms of the Peyrard-Bishop Hamiltonians proposed by Barbi et al. [5] and reduce them to their flattened 2D version by setting all torsional angles to zero. The resulting zero-angle (ZA) 2D Hamiltonian differs from the original Peyrard-Model Hamiltonian mainly by the inclusion of a helicoidal step distance $h$. The received wisdom is that this distance stays fixed at 3.4 Å for B-DNA. However, the base step, better known as rise distance, is far from constant and shows important dependencies with nearest neighbour context [6, 7, 8]. While for calculation purposes adding yet another fixed parameter to the Hamiltonian would appear to be of little advantage, here we have the opportunity to advance our understanding of DNA structural parameters by taking this additional parameter into account.

2. Model

Our interest is the study of the structural rise distance $h$. However this distance is not present in the original formulation of the Peyrard-Bishop model [1]. The 3D helicoidal variants of this Hamiltonian do incorporate the rise distance $h$, however melting temperature fitting methods [3] can presently deal only with 2D Hamiltonians. Therefore, our approach is to start from a 3D helicoidal Hamiltonian and then simplify this to a 2D Hamiltonian which can be used with melting temperature fitting methods.

The 3D Hamiltonian, derived from the Lagrangean proposed by Barbi et al. [5] without the last potential that models the stacking interaction, is

$$H_{n,n-1} = \frac{p_{r_n}^2}{4m} + \frac{p_{\phi_n}^2}{4mr_n^2} + D(\exp[-a(r_n - R_0)] - 1)^2 + k(l_{n,n-1} - l_0)^2. \tag{1}$$

Rewriting this torsional Hamiltonian [5] in the notation of the original PB model [1] and setting the angles to zero ($\phi_i = 0$ and $\theta_0 = 0$), we obtain a 2D Hamiltonian

$$H_{n,n-1} = \frac{q_n^2}{2m} + D(\exp[-a\sqrt{2}y_n] - 1)^2 + \kappa_{\alpha\beta} \left( \sqrt{h_{\alpha\beta}^2 + \frac{1}{2}(y_n - y_{n-1})^2} - h_{\alpha\beta} \right)^2 \tag{2}$$

where we used the distance between the bases of a pair $2(r_n - R_0) = \sqrt{2}y_n$, and the distance between neighbouring base pair

$$l_{n,n-1} = \sqrt{h_{\alpha\beta}^2 + (r_n - r_{n-1})^2}. \tag{3}$$

The distance between the planes of subsequent base pairs $h_{\alpha\beta}$ is now no longer a fixed value for the whole molecule but has become context dependent. For the remainder of this work we will call this new Hamiltonian the zero-angle (ZA) model.

With the Hamiltonian being now dependent on a single variable $y$, we are able to apply the framework of parameter minimization developed previously [3]. To obtain the values for rise distance $h_{\alpha\beta}$ we optimize these parameters by comparing the predicted melting temperature with the experimental data of DNA melting [9]. Even considering canonical base pairs only, it was necessary to vary ten elastic force constants $k$, ten step rise $h$ and two pairs of Morse potential parameters $D$ in a total of twenty-four parameters. Due to the large number of parameters the minimization was carried out in two steps. First we used a fixed rise distance $h = 3.4$ Å, and minimized all remaining parameters. In the second round of minimization we relaxed the constraint on the rise distance $h$, obtaining thus the final nearest-neighbour dependent values of rise distances.
3. Results

Figure 1 shows how the parameter rise depends on salt concentration for the DNA sequence CGATCGATCG according the ZA model. The influence of salt concentration is more pronounced for ApT steps, which are less hydrogen bonded than the other types of nearest-neighbours.

![Rise distance profile for the DNA sequence CGATCGATCG as function for all salt concentrations reported in [9].](image)

The comparison of our rise distances $h$, obtained from the modified Peyrard-Bishop ZA Hamiltonian, with experimentally determined values is not straightforward. The DNA structural parameters obtained from experimental techniques, such as X-ray diffraction and NMR, require extensive additional theoretical and algorithmic modelling. Figure 2 shows the comparison of rise distances obtained from our ZA model and various models for x-ray diffraction: CEHS [6], NEWHELIIX, 3DNA [7, 8]. These models used experimental data of X-ray images [10] to estimate the step parameters and arrive at seemingly conflicting results. According to Lu and Olson [11], this inconsistence is mainly due to different ways of describing the reference frame of the DNA helical structure. We noticed that although the qualitative behaviour of our ZA model is similar to CEHS and NH, quantitatively it is closer to the results of the newer 3DNA model [8].

We also compared calculated rise distances to experimental data of NMR measurements analysed by 3DNA for the sequence GGGCATGCTACGCG [12], shown in Fig. 3. In contrast to the X-ray data of Fig. 2, the NMR show a marked tendency towards smaller rise steps which are not followed by the results of the ZA model.

4. Conclusion

We presented a 2D mesoscopic model as new way to calculate the structural step parameters of a DNA sequence. The main difference here is the origin of the experimental data which are melting temperatures instead of X-ray diffraction or nuclear magnetic resonance. Comparison of our results with existing experimental measurements (X-ray, NMR) point toward the need to a consistent approach in the interpretation of the reference frame of the DNA helical structure. Further work is in progress for a complete comparison of our results and existing results in the Protein Database (PDB) as well as for the calculation of rise distances for RNA.

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Figure 2. Rise distance $h$ profile comparing the ZA model with various models for x-ray diffraction (CEHS, NEWHELIX and 3DNA).

Figure 3. Comparison of the modified Peyrard-Bishop ZA model and 3DNA models for the DNA sequence GCGCATGCTACGCG. These 3DNA results are based on NMR experimental data.

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