Evaluation of a Coarse-grained Model of DNA using Molecular Dynamics Simulations

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Abstract: Availability of experimental data now provides a basis for developing computer models to investigate mechanical events in biological systems. Herein, a coarse-grained model that attempts to remove all unnecessary degrees of freedom, while accurately predicting the entropic elasticity of DNA is presented. The model was evaluated with molecular dynamics simulations of super-coiled DNA uncoiling. In particular, the relative end-to-end extension (z/L) as a function of applied force was calculated. Comparison of model predictions with experimental data suggests that the coarse-graining employed represents a starting point for developing more useful models, in that relative DNA extension was accurately predicted for the low force limit while at higher forces the model failed.

Introduction: Many biological processes (e.g. intracellular trafficking, DNA replication, enzymatic cleavage, etc.) can be broken down into a combination of chemical and mechanical steps. For example, during DNA replication, DNA Helicase acts as an active motor to convert chemical energy from ATP hydrolysis into mechanical energy, which is then used to translocate along the DNA contour and unwind the DNA.[1] Indeed, understanding the interplay between these steps is crucial to improving our understanding of chemically-driven, mechanical processes, as well as our ability to manipulate and control these processes in cases where the wild-type behavior has been altered (i.e. diseased-states).

While much effort has been spent over the last few decades deciphering the chemical nature of these processes, researchers have relatively recently begun to explore the mechanical mechanisms involved. In fact, only with the development of high-resolution, single molecule techniques (e.g. optical and magnetic tweezers, atomic force microscopy, tethered force probe, etc.) has significant progress been made in understanding the mechanochemistry of biological processes.[1] Importantly, the availability of experimental data now provides a basis for developing accurate computer models to investigate the thermodynamics and kinetics of mechanical events in biological systems.

Herein, a simple coarse-grained model of DNA is presented. The model was evaluated by comparing results from molecular dynamics (MD) simulations to experimental data of the forces required to uncoil super-coiled DNA. This study represents the starting point for developing more complete models to aid in our investigation of biomechanical processes.

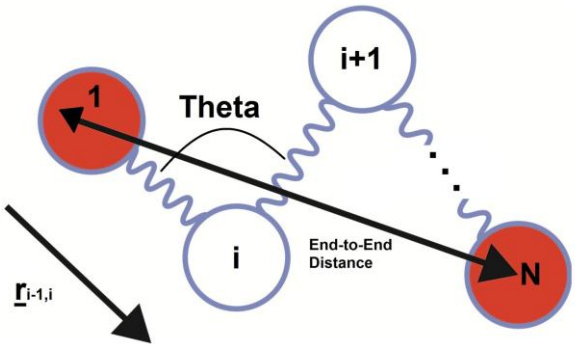

Figure 1 – Coarse-grained model of DNA.

Coarse-Grained Model: A single, 32.8 μm dsDNA polymer was modeled as a series of beads connected by harmonic springs, Figure 1. Importantly, previous studies indicate that the relevant energetic contributions to DNA coiling/uncoiling behavior relate to stretching, bending,

and electrostatic interactions[2]; therefore, the potential energy function (1) was chosen to reproduce these interactions, while all other energetic contributions were ignored.

$$(1)\ \frac{U}{k_BT} = \frac{U_{Bond}}{k_BT} + \frac{U_{Electrostatic}}{k_BT} + \frac{U_{Bend}}{k_BT}$$

In particular, a pairwise harmonic stretching potential (2), pairwise screened coulomb potential (3), and a three-body bending potential (4) were used. Parameters are given in Table 1.

$$(2)\ \frac{U_{Bond}}{k_BT} = \frac{\gamma}{2}\sum_{i=1}^{N-1}(r_{i,i+1} - r_0)^2$$

$$(3)\ \frac{U_{Electrostatic}}{k_BT} = \varepsilon \sum_{i=1}^{N-1}\sum_{j=2}^{N} \frac{e^{\frac{-r_{ij}}{\lambda_D}}}{r_{ij}}$$

$$(4)\ \frac{U_{Bend}}{k_BT} = \frac{\alpha}{2}\sum_{i=2}^{N-1}\left(cos^{-1}\left(\frac{\boldsymbol{r}_{i-1,i}\cdot\boldsymbol{r}_{i,i+1}}{r_{i-1,i}r_{i,i+1}}\right) - \pi\right)^2$$

Name	Symbol	Value	Units
Contour Length	L	32.8	μm
Number of Beads	N	25	
Stretch Constant	γ	365853	μm^{-2}
Bend Constant	α	0.0388	
Coulomb Constant[3]	ξ	46533	μm
Molarity	M	0.01	mol/liter
Debye Length	λ_D	$(10.8 * M)^{-0.5}$	nm
Temperature	T	310	K
Bond Length	r_0	L/(N-1)	μm
Bead Mass	m	$(1.047e^{-19})/N$	kg
Boltzmann Constant	k_B	$1.38e^{-23}$	J/K
End-to-End Distance	z		μm

Table 1 – Parameters used in MD simulations. All physically relevant parameters were taken from Marko and Siggia (1995) unless otherwise denoted.

Force equations were determined according to equation (5), but are not shown here (refer to the Fortran file for the exact force equations used).

$$(5)\ \boldsymbol{F}_i = -\frac{\partial U}{\partial \boldsymbol{r}_i}$$

The system was initialized by placing the beads an equilibrium distance apart, in a straight line, and small, random perturbations in the x and y coordinates were made to aid equilibration. The system was propagated in time using the velocity Verlet algorithm[4], and the system was maintained at constant temperature with an Anderson thermostat employing massive collisions[5]. Umbrella sampling was used to ensure significant sampling of the entire reaction coordinate, relative end-to-end distance (z/L). Briefly, one end of the polymer was rigidly tethered to its starting position by a harmonic potential, while the other end was loosely tethered by a harmonic potential, ($k_{rigid} >> k_{loose}$), some defined distance away. Each individual simulation was run at a defined tether distance; however, for each successive simulation the tether distance was increased. This ensured sufficient sampling of the entire reaction coordinate, $0 < z/L < 1$. The time-step and equilibration times were chosen so that energy was conserved and equilibration was achieved for any tether distance, Figure 2.

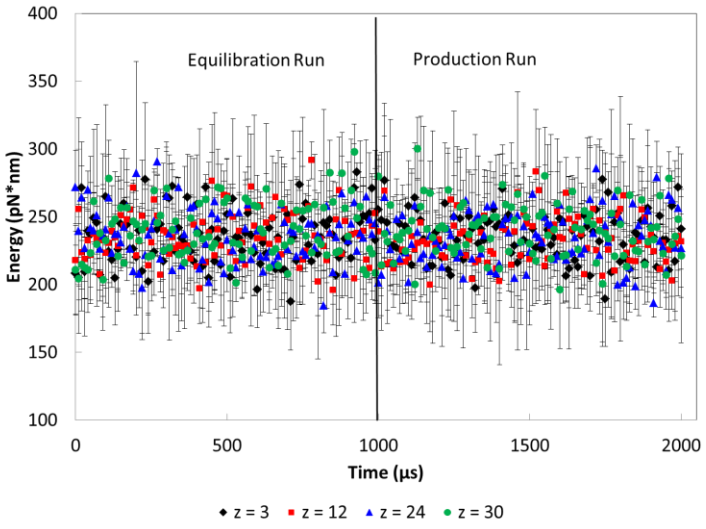

Figure 2 – Total energy during the equilibration run and production run for simulations sampling extensions along the reaction coordinate, z/L. Error bars represent the mean ± std.

Production runs were performed for 1000 μs and the end-to-end extension was recorded after each Anderson thermostat massive collision; velocity randomization was assumed to de-correlate bead positions. Three production runs were performed to generate enough data points for statistically sufficient histograms, Figure 3. This was repeated for tether distances from 3 – 30 μm, increased at increments of 1 μm. Weighted end-to-end distance probabilities were then unweighted[6], stitched together, and analyzed to generate a force vs. extension curve.

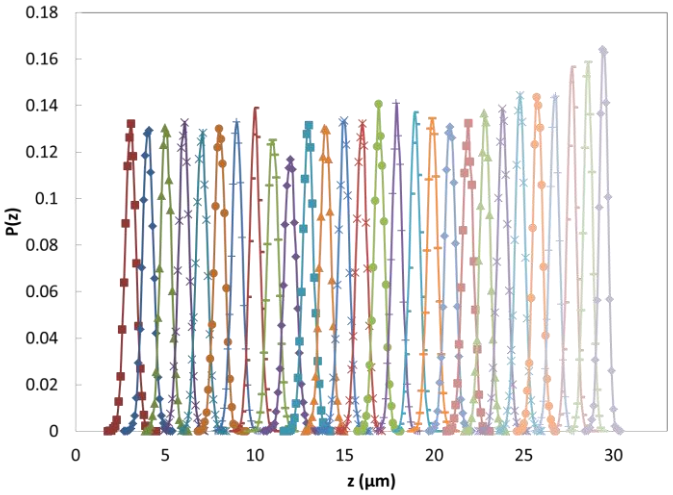

Figure 3 – Histograms of weighted end-to-end extension probabilities for simulations sampling extensions, $3 \leq z \leq 30$. Each histogram is based on three simulations and 12000 data points.

Results and Discussion: A force versus extension curve was generated from the probability distributions, Figure 4. The data shows extension increases linearly with force in all force regimes.

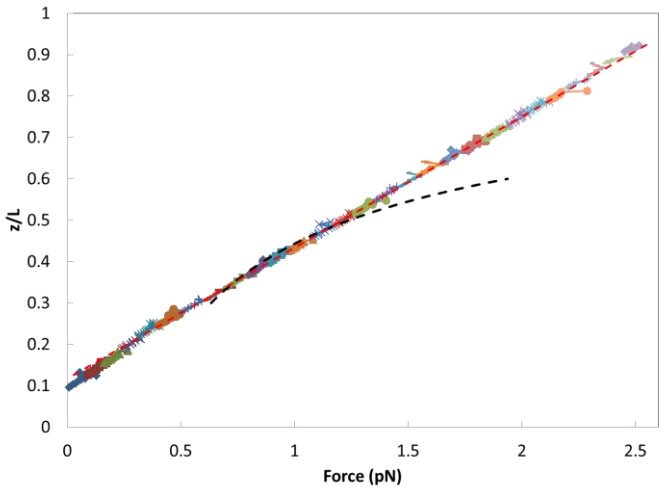

Figure 4 – Extension as a function of force. The colors represent the contributions from stitching together individual histograms. The dashed red line is a linear best-fit, $R^2 = 0.99$, and the dashed black line shows WLC scaling, $z/L \sim F^{-1/2}$.

Importantly, the model does accurately predict the appropriate scaling regime in the low force limit. Experimental data shows for $F < k_BT/A$, relative end-to-end distance scales linearly with force. However, as force is increased nonlinear entropic behavior should emerge, and z/L should scale with the inverse square root of the force.[2] This is not captured by the coarse-grained model.

Interestingly, the model predicts scaling behavior dissimilar to the analytical freely-jointed-chain (FJC) and worm-like-chain (WLC) models, for forces above k_BT/A. For the latter, this is most likely due to discretizing a continuous chain into 25 segments. Indeed, increasing the number of beads in the coarse-grained model is expected to result in more realistic behavior.

In conclusion, comparison of model predictions with experimental data suggests that the coarse-graining employed represents a starting point for developing more useful models. Relative DNA extension was accurately predicted for the low force limit while at higher forces the model failed. Improvements to the model could include increasing the number of beads, adding a wall potential to account for DNA-bead interactions present during experiments, or changing the potentials used, to more completely represent the potential energy landscape of DNA.

Movie: The movie shows a coarse-grained DNA strand uncoiling. One end is tethered while a force is applied to the other end (red atoms). The end-to-end extension increases as the force is increased.

References:

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