

Computer Modeling of DNA Unknotting by TypeII Topoisomerases

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Type II topoisomerases (Topo II) are essential enzymes common to all organisms. Their cellular functions include maintaining the levels of chromosome supercoiling and ensuring proper segregation at cell division. Topo II performs strand passage on its substrate DNA. This action has been well characterized at the molecular level [2]. Topo II binds a dsDNA segment called the G-segment, it introduces a double strand break on the G-segment allowing the passage of another DNA fragment called the T-segment. The break is resealed, and both T and G segments are released. When acting on knotted DNA molecules TopoII is known to unknot DNA below thermodynamic equilibrium [3]. That is, the steady-state fraction of knotted molecules produced by topoII is much lower than that obtained by random cyclization of linear DNA (which depends only on the conformations adopted by DNA in solution)[3]. Different biophysical models have been proposed to explain this phenomenon [4][5][6].

Here we address the question of whether the crossings acted on by topoII are selected at random or not (illustrated in Figure 1). Our study is based on Monte-Carlo computer simulations of DNA unknotting.

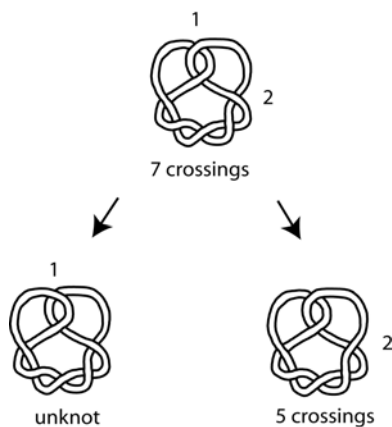


Figure 1: The figure shows two possible strand-passage events on a 7-crossing twist knot K . The pathway on the left indicates one strand-passage at the location “1” taking the 7-crossing K to the unknot in one step. The pathway on the right converts K into a 5-crossing knot by performing strand-passage at the location “2”, thus three of these events are required to reach the unknot.

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We model the action of topo II as a finite state Markov chain in which each state is a knot type (with crossing number less than 8) and whose transition probabilities are estimated by Monte-Carlo computer simulations of random strand-passage on knotted molecules of fixed length. DNA molecules are modeled as a polygonal chain in the simple cubic lattice and their state space is sampled using the BFACF algorithm [1]. Strand passage simulations are performed symbolically at the Dowker-code level (an integer-entry vector whereby each entry is assigned to a crossing on a fixed knot projection). To each knot K corresponds an infinite family of Dowker-codes D_k with $n, n+1, n+2, \dots$ entries where n is the crossing number for K . However to each embedding of the knot K , with fixed length L , corresponds a finite subfamily $D_{K,L}$ and a probability distribution $P_{K,L}$ that assigns a probability to each Dowker code. We use BFACF to generate the pair $(D_{K,L}, P_{K,L})$ as a function of K and L . Given $(D_{K,L}, P_{K,L})$, we simulate random strand passage on K . We compute the transition probabilities of the Markov chain by repeating the strand-passage simulation until convergence is achieved.

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