

Modelling State Transitions in Knot Space Motivated by Type II Topoisomerase Action

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ABSTRACT

Type II topoisomerases are enzymes that simplify the topology of DNA very efficiently by performing strand-passage. Motivated by this experimental observation, We aim to investigate the effect of random strand-passage between knots of the same length and different types. We use the BFACF algorithm to generate polygons of a fixed knot type in Z^3 . Then we introduce an efficient strand-passage algorithm which gives rise to a Markov chain of transitions between knot types whose steady state distribution can be compared to experimental data.

Mathematical Subject Classification 2000: 57; 60; 92

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Type II topoisomerases are enzymes that mediate the passage of two double-stranded DNA segments through each other by creating a transient double-strand break in one of the segments [8, 9]. Type II topoisomerases are essential to every living organism, and are excellent targets for anti-bacterial and anti-cancer drugs (*e.g.* [1]). They play important roles during cellular processes such as DNA replication and transcription. More generally they control undesired changes in the topology of chromosomes and naturally occurring plasmids. It has been shown experimentally that type II topoisomerases simplify DNA topology below thermal equilibrium values [10]. In this work we are interested in the process of DNA unknotting by type II topoisomerases.

Motivated by experimental observations, we investigate the effect of random strand-passage between knots of same length and different types. Our long term goal is to simulate, using mathematical and computational methods, the process of DNA unknotting by type II topoisomerases. First we simulate state-transitions in knot space resulting from random strand-passage not subject to any topological biases. This work has been reported in detail in [2]. Deviations from randomness observed experimentally suggest possible topological biases which result in better match with the experimental data (*e.g.* [10, 13, 4]). We are currently working on the implementation

of different topological biases. Here follows a brief description of the work completed so far.

We use the BFACF algorithm to generate ensembles of polygons in Z^3 of a fixed knot type K and lengths within a specified range $L \pm e$, where L is the mean length obtained by fixing the fugacity per bond, and e is a small range of error [5, 7]. We take multiple projections of each knot type in random directions and obtain a list of Dowker-Thistlethwaite codes (DT codes) from these projections. This step reduces the complexity of the simulation by replacing the coordinate files with a list of relatively short integer entry vectors which characterize each knot type. Notice that the DT codes can be compared to snap-shots which keep track of the chain as it moves in space. We introduce a novel strand-passage algorithm which operates at the DT code level. We perform random strand-passage by changing the sign of a randomly chosen entry in a DT code, and use the HOMFLY polynomial to identify knot types after random strand-passage. At the end of this process we obtain the transition probability matrix $P_{L \pm e}$ which specifies one-step transition probabilities between knot types. Powers of the transition matrix give information on the distribution of knot types after repeated strand-passage events. The limit distribution (steady-state) can be compared to experimental values.

The stationary state in our simulations currently gives knotting probabilities larger than those experimentally observed for DNA in solution. To solve this problem, we aim to simulate long enough polygons in Z^3 with the bending properties of DNA [12] and reproduce computational and experimental data on random knotting probabilities [3, 11]. Furthermore we will implement various biases to the strand-passage simulation and compare our results to experimental data on unknotting by type II enzymes.

In addition we have made calculations of minimal number of sticks needed to realize a knot in the simple cubic lattice, and have improved existing bounds [6]. We have also done calculations, to be reported elsewhere, of average crossing number, writhe, and strand-passage distances between prime knots with 8 or less crossings.

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