COMPUTER MODELING OF DNA UNKNOTTING BY TYPE II TOPOISOMERASES

Barath Raghavan[1], Diana Nguyen[2], Javier Arsuaga[3], and Mariel Vazquez[4]

Keywords: Topoisomerase II, DNA knots, polymer models, BFACF algorithm

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. When the break is resealed, both T and G segments are released. When acting on knotted DNA molecules, Topo II is known to unknot DNA below thermodynamic equilibrium [3]. That is, the steady-state fraction of knotted molecules produced by Topo II is much lower that 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 Topo II are selected at random or not (illustrated in Figure 1). Our study is based on Monte-Carlo computer simulations of DNA unknotting.

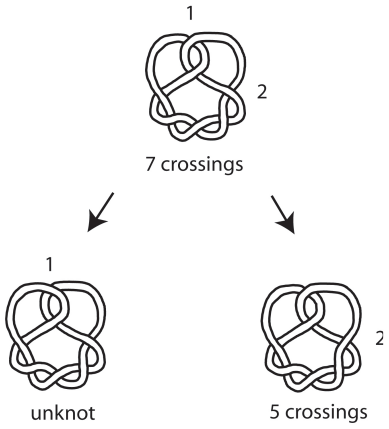

Figure 1: Two possible strand-passage events on a 7-crossing twist knot K. The pathway on the left indicates one strand-passage at the location "1" taking the 7-crossing knot K to the unknot in one step. The pathway on the right converts K into a 5-crossing knot by performing strand-passage at location "2", thus requiring three such events to reach the unknot.

[1]Department of Computer Science and Engineering, University of California, San Diego
[2]Department of Bioengineering, University of California, Berkeley
[3]Cancer Research Institute, University of California, San Francisco
[4]Department of Mathematics, University of California, Berkeley

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 polygonal chains 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 $n, n+1, n+2, \ldots$ 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.

References

[1] Madras, N. and Slade, G. 1993. The self-avoiding walk. Boston Birkhauser

[2] Roca, J., Berger, J.M., Harrison, S.C., Wang, J.C. 1996. DNA transport by a type II topoisomerase: direct evidence for a two-gate mechanism. Proceedings of the National Academy of Sciences USA. 93(9): 4057-62

[3] Rybenkov, V.V., Ullsperger, C., Vologodskii, A.V., Cozzarelli, N.R. 1997. Simplification of DNA topology below equilibrium values by type II topoisomerases. Science. 277(5326):690-693.

[4] Trigueros, S., Salceda, J., Bermzdez, I., Fernandez, X and Roca, J., 2004 Asymmetric removal of supercoils suggests how topoisomerase II simplifies DNA topology. Journal of Molecular Biology 335:723-731.

[5] Vologodskii, A.V., Zhang, W., Rybenkov, V.V., Podtelezhnikov, A.A., Subramanian, D., Griffith, J.D., Cozzarelli, N.R. 2001. Mechanism of topology simplification by typeII DNA topoisomerases. Proceedings of the National Academy of Sciences USA 98(6)3045-49:5849-5856.

[6] Yan, J., Magnasco, M.O., Marko, J.F. 1999. A kinetic proofreading mechanism for disentanglement of DNA by topoisomerases. Nature 401(6756):932-935