New and Notable

Protein-Assisted DNA Looping: A Delicate Balance among Interactions, Mechanics, and Entropy

Anatoly B. Kolomeisky[1,*]
[1]Department of Chemistry and Center for Theoretical Biological Physics, Rice University, Houston, Texas

DNA looping is a unique process demonstrated when two distant sites on the biopolymer molecule bind. It is frequently observed in living systems where DNA looping is critically important for many cellular processes, including gene expression and regulation, DNA replication and recombination, DNA repair, chromosome segregation, and many others (1,2). In nature, the formation of cyclic DNA or DNA with loops is usually assisted by various types of protein molecules. A simultaneous binding of a single protein molecule to two different binding sites on DNA creates a loop. Protein-DNA interactions help to stabilize these loops. Many experimental and theoretical studies have been devoted to understanding the mechanisms of DNA looping and cyclization (2–4). Although thermodynamic driving forces of the process are now well established, the dynamic picture of loop formation is much less clear (2–7).

Contemporary theoretical views of DNA looping concentrate on the effect of elastic properties of DNA and on the role of assisting proteins in the kinetics of the process (3,5–7). The central quantity of many investigations is a Jacobson-Stockmayer factor, or *J*-factor, which comes from fundamental theoretical studies of polycondensation chemical reactions (8). The *J*-factor is usually associated with the concentration of free ends, and in experiments it is measured as a ratio of binding and unbinding rates (4,6). Because this ratio is given as the exponential of the free-energy difference between the looped and unlooped states, the *J*-factor also effectively describes the equilibrium constant for a looping or cyclization chemical reaction. Thus, for large *J*-factors the probability of creating loops is high, while for small values of the *J*-factor the DNA molecule prefers to be free with unconstrained sites. Because the *J*-factor is viewed as a concentration of free DNA ends, it is usually assumed that only the looping or association reaction is affected by changes in the *J*-factor. However, recent experiments clearly show that dissociation rates are also coupled to the *J*-factor (9). This suggests that there are additional factors that influence the dynamics of the loop formation in DNA. The article by Mulligan et al. (9) in this issue of the *Biophysical Journal* presents a new theoretical model that successfully explains many dynamic features of DNA looping.

The theoretical approach of Mulligan et al. (9) explicitly takes into account protein-DNA interactions, DNA mechanics, and conformational entropy in order to develop a comprehensive dynamic description of the process. The main advantage of the model is that it is simple enough to provide analytical calculations while capturing the most relevant physical-chemical features of the system. It explicitly calculates the free-energy landscape of DNA looping by considering DNA as a semiflexible polymer, with short-range protein-DNA interactions at the binding sites that also resist bending and twisting. This theoretical model estimates the *J*-factor and connects the free-energy profiles with kinetics of polymer looping. Mulligan et al. (9) found that for short DNA chains the loop formation kinetics is a rate-limited one, limited by high energetic costs of bending and twisting; whereas increasing the range of protein-DNA interactions accelerates the association of two DNA sites into the loop. The elastic properties of DNA and protein-DNA interactions become less important for longer DNA chains.

But the most important achievement of Mulligan et al. (9) is the observation that mean lifetimes in both looped and unlooped states depend on the *J*-factor. This theoretical model challenges today's theoretical views (10) that the dissociation rate (or the looped lifetime) should not be affected by the *J*-factor. This fundamentally important result also provides new details in the microscopic description of the looping processes. Previous theoretical methods (10) implicitly assume that the position along the reaction coordinate, and the free-energy height of the transition state in the loop dissociation reaction, are not affected by the free-energy changes in the looped and unlooped states, i.e., that they are independent of *J*-factor. However, explicit calculations of Mulligan et al. (9) clearly show that the position and the amplitude of the kinetic barrier, as well as free energies for the looped and unlooped states, depend on the range of protein-DNA interactions and on the elastic properties of DNA. This leads to theoretical predictions on the strong correlations with the *J*-factor, which agree with experimental observations.

Although the theoretical model of Mulligan et al. (9) provides a significant advance in our understanding of fundamental processes during DNA looping and cyclization, it is important to note that many questions remain unanswered and many details are still not explained. This approach neglects the sequence specificity of DNA chains, which might be important for more-realistic descriptions of bending and twisting. Furthermore, the coupling of bending and twisting degrees of freedom is not considered. The model

Submitted May 20, 2015, and accepted for publication June 8, 2015.

*Correspondence: tolya@rice.edu

Editor: Keir Neuman.

0006-3495/15/08/0459/2

http://dx.doi.org/10.1016/j.bpj.2015.06.055

also does not account for the effects of polymer relaxation, and as a result the behavior of long DNA chains is not correctly captured by this method. Another important dynamic process not discussed in this theoretical model is how the protein-bound DNA site finds another specific site to create a loop. It is known that protein search for specific sites on DNA is a complex process that involves intermediate bindings to other nonspecific sites on DNA with consequent sliding along the DNA (11,12). This might strongly affect the dynamics of DNA looping. Despite these issues, the work of Mulligan et al. (9) is a large step forward in our understanding of DNA looping processes, which clarifies many dynamic features of the process. This is also an example of outstanding theoretical work that successfully applies fundamental concepts in Physics and Chemistry for analyzing complex biological phenomena.

REFERENCES

1. Schleif, R. 1992. DNA looping. *Annu. Rev. Biochem.* 61:199–223.
2. Cournac, A., and J. Plumbridge. 2013. DNA looping in prokaryotes: experimental and theoretical approaches. *J. Bacteriol.* 195: 1109–1119.
3. Toan, N. M., G. Morrison, …, D. Thirumalai. 2008. Kinetics of loop formation in polymer chains. *J. Phys. Chem. B.* 112: 6094–6106.
4. Du, Q., C. Smith, …, A. Vologodskii. 2005. Cyclization of short DNA fragments and bending fluctuations of the double helix. *Proc. Natl. Acad. Sci. USA.* 102:5397–5402.
5. Merlitz, H., K. Rippe, …, J. Langowski. 1998. Looping dynamics of linear DNA molecules and the effect of DNA curvature: a study by Brownian dynamics simulation. *Biophys. J.* 74:773–779.
6. Cloutier, T. E., and J. Widom. 2004. Spontaneous sharp bending of double-stranded DNA. *Mol. Cell.* 14:355–362.
7. Zhang, Y., A. E. McEwen, …, S. D. Levene. 2006. Statistical-mechanical theory of DNA looping. *Biophys. J.* 90:1903–1912.
8. Jacobson, H., and W. H. Stockmayer. 1950. Intramolecular reactions in polycondensations. 1. The theory of linear systems. *J. Chem. Phys.* 18:1600–1606.
9. Mulligan, P. J., Y. -J. Chen, …, A. J. Spakowitz. 2015. Interplay of protein binding interactions, DNA mechanics, and conformational entropy in DNA looping kinetics. *Biophys. J.* 109:618–629.
10. Allemand, J. F., S. Cocco, …, G. Lia. 2006. Loops in DNA: an overview of experimental and theoretical approaches. *Eur. Phys. J. E Soft Matter.* 19:293–302.
11. Kolomeisky, A. B. 2011. Physics of protein-DNA interactions: mechanisms of facilitated target search. *Phys. Chem. Chem. Phys.* 13:2088–2095.
12. Veksler, A., and A. B. Kolomeisky. 2013. Speed-selectivity paradox in the protein search for targets on DNA: is it real or not? *J. Phys. Chem. B.* 117:12695–12701.