Evaluating the role of coherent delocalized phonon-like modes in DNA cyclization

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The flexibility of the DNA molecule plays an important role in a multitude of biological functions as well as in the compact storage of the genetic material of cells. For example, the genome in each eukaryotic cell is tightly packed by sharply bending DNA around nucleosome and, similarly, DNA bending by transcription factors is a common cellular mechanism that participates in the regulation of gene expression. In the majority of cases, bending of DNA results in the formation of highly curved loops. The existence of these loops challenges the classical polymer physics view, in which double-stranded DNA is virtually unbendable at scales below its persistence length. Experimentally, the innate flexibility of the DNA molecule, is quantified by the so-called Jacobson-Stockmayer's J-factor, that represent the probability for cyclization. Recent experimental studies of ultra-short DNA sequences revealed a discrepancy of up to six orders of magnitude between the measured and predicted J-factors. These large differences suggested that, in addition to the elastic moduli, other factors, such as *intrinsic curvature* and *propensity for local melting* (aka DNA bubbles) can contribute to the loop formations.

In a study, published this week in Scientific Reports, we reported a new computational approach for evaluating DNA cyclization by linking the physics of *intrinsic curvature and 3D structure* with physics of *local melting*. The idea is that thermal fluctuations induce local strand separation resulting in short single stranded DNA regions of the otherwise doubled-stranded rigid molecule. These regions act as effective hinges in the rigid molecule and thus significantly enhance DNA flexibility. Our new model is for the first time able to quantify these effects in an explicit sequence dependent manner. We apply the new model to all DNA sequences whose J-factors have previously been experimentally characterized. Our analysis demonstrates that the model is able to accurately determine the J-factors of ultra-short DNA sequences with most predictions being within an order of magnitude of experimental measurements. Further, our model also accurately describes the J-factors of longer sequences, and we demonstrate that this model is applicable to experimental DNA sequences containing a base pair mismatch.

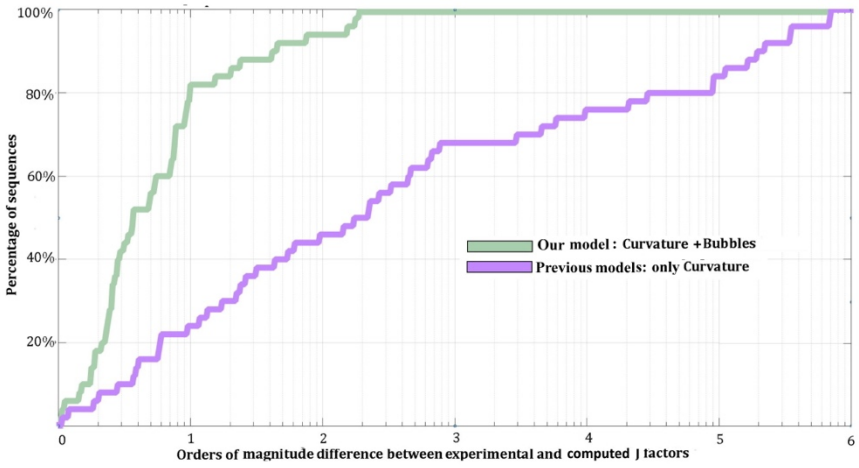

Figure 1. *Estimated J-factors for DNA sequences with lengths shorter than 100bp. The two different curves with colors correspond to: (purple) The previous well-established DNA model that account for 3D structure and curvature (Czapla, L., Swigon et al., 2006, JCTC; Alexandrov et al., 2016, BMC Bioinformatics); and (green) to our model, reported this week in Scientific Reports. The y-axis reflects the orders of magnitude difference between experimentally measured and computationally derived J-factors. The x-axis corresponds to the percentage of sequences for a given order of magnitude difference.*

Our model yields more than 82% of the calculated J-factors within an order of magnitude of experimental measurements, while the analysis of J-factors for sequences longer than 100bp shows that it gives results indistinguishable from the results obtained by previous models **Fig. 1**.

The reported work, for the first time, supports a direct link between sequence-dependent bubbles and an accurate calculation of J-factors for short DNA segments. In addition, considering recent experimental observations demonstrating that DNA bubbles are indeed in the terahertz range, leads to an exciting avenue for future exploration of J-factors in the presence of a strong, pulsed terahertz field. Such future studies will allow elucidation of the connection between terahertz irradiation and DNA functionality.

References

Alexandrov et al., Scientific Reports, 2017, http://rdcu.be/vnuI

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