

Nucleic Acids Chemistry beyond the Watson-Crick Double Helix (70) : Prediction of DNA duplex stability having biased base compositions under molecular crowding conditions

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Base composition of the DNA largely varies across the genome and it was often found that important functional regions of genome contain biased composition of bases such as consecutive guanine/cytosine (GC) and adenine/thymine (AT) tracts. Such biased DNAs play decisive roles in many important biological reactions including gene replication and expression in cell. For example, depending on their stability in cell, GC-biased duplex DNAs form noncanonical structures in promoters and telomeres that influence gene expression.¹ Therefore, for understanding and regulating the biological processes related to these sequences, it is crucial to predict the stability of biased DNA duplexes in cell-like environments. In this study, we investigated the thermodynamic stabilities of biased DNA duplexes under the cell-mimicking crowding condition using the nearest-neighbor (NN) model that defines the duplex stability from the sequence of NN base pairs.² We observed that biased DNAs were remarkably more stable than the predicted stability using NN prediction parameters for the crowding condition in physiological salt concentration (Figure 1). Thermodynamic analyses suggested a different state of hydration around the biased duplexes compared to unbiased sequences under molecular crowding conditions, that restricted thermodynamic prediction using existing NN parameters. To correct the NN prediction, we introduced new parameters termed as ‘hydration factors’ into NN parameters that enabled accurate thermodynamic prediction for any DNA sequences including biased DNA sequences in crowded environments. Our novel prediction method will be important for their biotechnological applications related to crowded environments and also for understanding the structural equilibrium in telomeres.

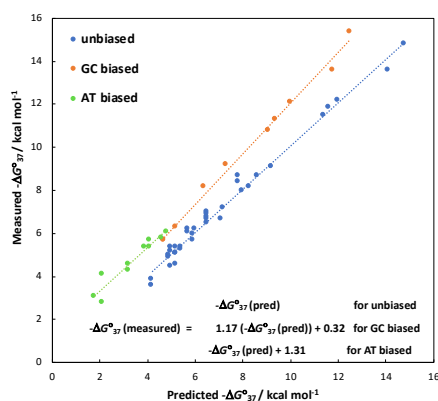


Figure 1. Plot of measured ($-\Delta G^{\circ}_{37}$) vs. predicted ($-\Delta G^{\circ}_{37}$) for unbiased (blue points), GC-biased (orange points) and AT-biased (green points) DNAs in the presence of 40 wt% PEG 200 at 100 mM NaCl with 10 mM Na_2HPO_4 and 1 mM Na_2EDTA .

- 1) M. L. Bochman et al., *Nat. Rev. Genet.* **2012**, 13, 770. 2) a) I. Tinoco, Jr. et al., *Nat. New Biol.* **1973**, 246, 40. b) S. Ghosh, N. Sugimoto et al., *Proc. Natl. Acad. Sci. USA* **2020**, 117, 14194.