Shape and Dynamics of Transcription Factor Binding Sites

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Sequence-specific transcription factor binding relies on two distinct mechanisms of sequence readout: base-wise readout based on sequence-specific hydrogen bonding patterns and a by now poorly understood process called indirect readout relying on shape and deformability of DNA. In case of Hox family transcription factors it was shown that subtle changes in DNA sequence distort local DNA shape and therefore disrupt transcription factor binding [1]. Three-dimensional shape of DNA was found to be even more conserved evolutionary than pure one-dimensional sequence information implying a fundamental function in DNA recognition [2].

B-DNA dodecamers containing sequence permutations of four central AT and flanking GC base pairs were simulated as model systems for transcription factor binding sites using AMBER 10 to investigate the impact of small changes in DNA sequence on shape and dynamics. Molecular dynamics simulations of 10 ns show large differences in minor groove width between the individual sequences, an important factor for amino acid side chain insertion possibility. Pure A-tracts show a narrower minor groove than sequences containing TpA-steps, reproducing effects observed in NMR experiments [3]. Moreover, the latter sequences show additional conformational flexibility, which presumably causes the reduced affinity for groove binding [4] and side chain insertion of arginine and lysine residues [5].

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[1] R. Joshi, J. M. Passner, R. Rohs, R. Jain, A. Sosinsky, M. A. Crickmore, V. Jacob, A. K. Aggarwal, B. Honig, R. S. Mann, *Cell*, **2007**, *131*, 530-543.
[2] S. C. J. Parker, L. Hansen, H. O. Abaan, T. D. Tullius, E. H. Margulies, *Science*, **2009**, *324*, 389-392.
[3] R. Stefl, H. Wu, S. Ravindranathan, V. Sklenar, J. Felgon, *PNAS*, **2004**, *101*, 1177-1182.
[4] F. A. Tanious, D. Hamelberg, C. Bailly, A. Czarny, D. W. Boykin, W. D. Wilson, *JACS*, **2004**, *126*, 143-153.
[5] R. Rohs, S. M. West, A. Sosinsky, P. Liu, R. S. Mann, B. Honig, *Nature*, **2009**, *461*, 1248-1254.