Mechanisms of Direct and Indirect Readout[≠]

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Based on high-resolution 3D structures, we are developing predictive models of direct and indirect readout of DNA sequence by proteins. *Indirect Readout; Reading DNA Sequence at a Distance.* The non-contacted bases in the centers DNA complexes of the 434 repressor, P22R and other HTH proteins are important determinants of affinity. These proteins can induce transitions from B-DNA to B'-DNA, which is characterized by a narrow minor groove and a zig-zag spine of hydration. The sequence is read by a sensing of the free energy of the transition from B- to B'-DNA, which depends on sequence. Thus, protein affinity is determined by known relationships between DNA sequence, conformation and hydration. *Direct Readout; Reading DNA Sequence by Direct Interactions.* DNA sequence can be read directly by shape complementarily. Therefore non-directional van der Waals interactions between protein and DNA confer sequence-specificity. For example a valine reside can occupy a cleft formed by four methyl groups on sequential base pairs of 5' TTAA 3'. The cleft is intrinsic to the DNA sequence and does not arise from protein-induced DNA conformational change. Hydrogen bonding can play a secondary role in specificity.