The sequence-dependent structure and deformability of DNA play a major role for binding of proteins and regulation of gene expression. So far, most efforts to model DNA flexibility are based on unimodal harmonic stiffness models at base-pair resolution. However, multimodal behavior due to distinct conformational substates also contributes significantly to the conformational flexibility of DNA, further complicated by correlations to nearest-neighbor substates. We solve this challenge by combining a multivariate harmonic approximation with an Ising model for the substates and demonstrate the performance of the model on applications to DNA fluctuations and protein–DNA complexes. Our approach offers a wide range of applications to determine sequence-dependent deformation energies of DNA and to investigate indirect readout contributions to protein–DNA binding and DNA repair. In a second part all-atom Molecular Dynamics free energy simulations with a global twist restraint on DNA will be presented going beyond equilibrium fluctuations. The onset of a non-uniformly distributed deformation energy and a long-range correlation of helical parameters along the whole DNA molecule is observed allowing for long-range communication. With further unwinding an abrupt phase transition to a specific melting of a TATA box transcription start segment is observed. The results on unwinding and melting are also compared to an Ising model based only on experimental parameters. Finally, advanced sampling applications to follow a protein-ligand binding process facilitated by DNA deformations will also be presented.