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Modeling Charge Transfer in EndoIII-DNA: A Data-Driven Computational Approach

Filipe Camargo Dalmatti Alves Lima[1], Ayaz Hassan[2,3], Frank Nelson Crespilho[2]
[1]*Federal Institute of Education, Science, and Technology of São Paulo, Campus Matão, SP, Brazil*
[2]*São Carlos Institute of Chemistry, University of São Paulo, SP, Brazil*
[3]*IRCBM, COMSATS University Islamabad (CUI), Lahore, Pakistan*
e-mail address: fdlima@ifsp.edu.br

The redox-switchable [4Fe4S] cluster in Endonuclease III (EndoIII) plays a central role in DNA-mediated charge transfer (DNA-CT) during base excision repair. By toggling between oxidized and reduced states, EndoIII dynamically modulates its DNA binding affinity, enabling long-range communication essential for genome surveillance. Understanding this redox-regulated mechanism at the atomic scale provides not only fundamental insights into DNA repair but also pathways for developing sustainable, bioelectronic platforms. Here, we present an integrated computational and data-driven investigation that reveals how structural, vibrational, and electrochemical properties of EndoIII evolve upon DNA interaction.

Using density functional theory (DFT), we evaluated changes in Fe–S bond lengths, force constants, and vibrational frequencies of the [4Fe4S] cluster in both isolated and DNA-bound states. The calculations reproduced experimentally observed far-IR spectral shifts, especially the downshifting of Fe–S(thiolate) vibrational modes from 363 to 352 cm^{-1}, which indicates bond weakening and increased covalency—factors favoring stabilization of the $[4Fe4S]^{3+}$ oxidation state. These structural reconfigurations are supported by B-factor and Ramachandran analysis of X-ray structures, revealing that DNA binding reduces the conformational freedom of the protein, consistent with a more rigid, redox-active complex [1].

Machine learning models trained on FTIR-derived spectral features accurately predicted protein–DNA binding distances, with values ranging from 7.0 to 16.0 Å. Feature importance analysis pinpointed vibrational markers, such as phosphate stretching and CH out-of-plane bending, as strong predictors of spatial proximity. This allowed us to directly link changes in infrared fingerprints to functional binding geometry. Additionally, we quantified a ~150 mV shift in redox potential upon complexation, confirming electrochemical stabilization of the oxidized state and reinforcing the hypothesis of a redox-guided DNA scanning mechanism [2].

These findings offer a unified view of structure-function relationships in metalloprotein-mediated charge transfer, where geometry, redox tuning, and DNA conformation are intricately coupled. We also observed disruption of vibrational modes associated with the deoxyribose ring and phosphate backbone upon binding, aligning with prior models of base eversion and helix distortion during lesion recognition.

Together, our simulations provide molecular-level evidence that DNA binding induces electrostatic and geometric perturbations favoring [4Fe4S] oxidation [3,4]. These shifts not only enhance protein–DNA affinity but enable electron flow through the DNA duplex, a redox communication mechanism that underlies lesion detection. Our results link electronic structure modulation to biological function and enable the rational design of redox-active biomolecular sensors through computer simulations and data-driven analysis.

References:

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