Activation Mechanism of Transcription Factor MntR from the Bacterium *Halalkalibacterium halodurans* for DNA Binding

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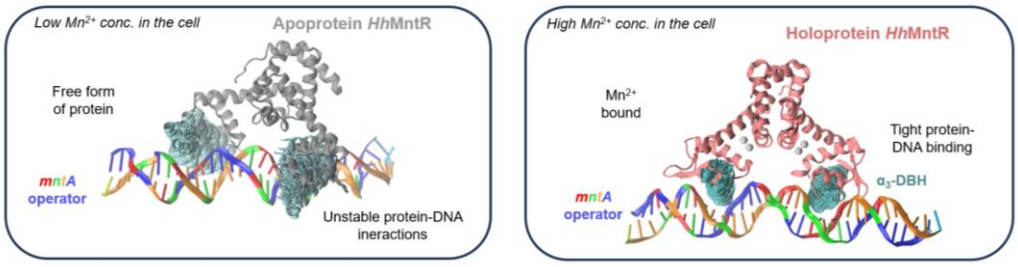
Transition metals, including iron, zinc and manganese, are essential for the survival of bacteria. The MntR protein (*Hh*MntR) plays a pivotal role in regulating manganese ion (Mn^{2+}) homeostasis in the bacterium *Halalkalibacterium halodurans*. To explore the structural and dynamic properties of various forms of *Hh*MntR upon Mn^{2+} binding, long-range all-atom molecular dynamics (MD) simulations were conducted, ranging from 500 ns to 1.25 µs. These simulations uncovered an allosteric mechanism triggered by Mn^{2+} binding, which modifies the non-covalent interaction network within the protein structure. This alteration results in a conformational change that significantly impacts the positioning of the DNA binding domains, thereby affecting the DNA binding affinity of *Hh*MntR [1]. In the next phase of research, the obtained structures of *Hh*MntR were aligned with DNA sequence corresponding to *mntA* operator by molecular docking. MD simulations of the resulting *Hh*MntR-DNA complexes provided valuable insights into the molecular interactions occurring between *Hh*MntR and DNA. The free *Hh*MntR exhibited highly dynamic behavior, frequently attaching to and detaching from the DNA backbone and inner grooves on a nanosecond timescale. In contrast, *Hh*MntR with Mn^{2+} in the binding site established stable and consistent non-covalent interactions with DNA. Similar behaviors were observed even in simulations that commenced with the protein separated from DNA by additional 10 Å to simulate complex formation. Moreover, key amino acids that contribute to the formation of the *Hh*MntR-DNA complex were identified, leading to the development of a molecular framework that facilitates *Hh*MntR's function as a transcription factor. Overall, the observed behaviors enhance the lateral movement of *Hh*MntR along the DNA sequence, allowing the protein to remain in proximity to the DNA while searching for specific base pairs to bind strongly upon activation by Mn^{2+} [2].



References:

[1] A. M. Knez, M. Manenica, Z. Jelić Matošević, B. Bertoša, *J Biomol Struct Dyn* (2024) DOI: 10.1080/07391102.2024.2314265.

[2] M. Manenica & B. Bertoša, *Int J Biol Macromol* 142937 (2025)