

Abstract Submitted
for the MAR11 Meeting of
The American Physical Society

Copper attachment to prion protein at a non-octarepeat site

MIROSLAV HODAK, North Carolina State University, JERRY BERNHOLC — Prion protein (PrP) plays a causative role in a group of neurodegenerative diseases, which include “mad cow disease” or its human form variant Creutzfeld-Jacob disease. Normal function of PrP remains unknown, but it is now well established that PrP can efficiently bind copper ions and this ability has been linked to its function. The primary binding sites are located in the so-called octarepeat region located between residues 60-91. While these are by now well characterized, the sites located outside these region remain mostly undetermined. In this work, we investigate the properties of Cu binding site located at His 111 using recently developed hybrid Kohn-Sham/orbital-free density functional simulations. Experimental data indicate that copper is coordinated by either four nitrogens or three nitrogens and one oxygen. We investigate both possibilities, comparing their energetics and attachment geometries. Similarities and differences with other binding sites and implications for PrP function will also be discussed.

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Date submitted: 19 Nov 2010

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