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Mechanistic insight into oxygen diffusion in prolyl hydroxylase domain-2 by equilibrium and non-equilibrium, classical and *ab initio* molecular dynamics simulations

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Abstract: The human oxygen sensing cycle characterizes the physiological regulation and detection of oxygen levels in mammals. It is now well-established that a relationship between the misregulation of human oxygen sensing and disease exists, including many types of cancers, ischemic and autoimmune diseases. In this computational study, molecular oxygen diffusion and the interactions of two key components of this cycle have been studied. The hypoxia-inducible factor (HIF) is the central signaling peptide of the cycle, regulated by a *trans*-4-hydroxylation reaction. Among the various proteins that are involved is prolyl hydroxylase domain-2 (PHD2), a member of the 2OG-dependent dioxygenase family of enzymes that uses molecular oxygen to catalyze a posttranslational hydroxylation reaction in the human oxygen sensing cycle

A combined approached involving classical molecular dynamics simulation trajectories comprising equilibrium and non-equilibrium MD together with *ab initio* molecular dynamics and QM/MM calculations has been employed to characterize oxygen transport and the mechanism of reaction of HIF and PHD2; a slow rate of was obtained, involving oxygen diffusion through an 8.0 Å wide oxygen pathway into the PHD2 active site lined by hydrophobic residues. The kinetic model proposed compares with experimental $k_{cat}(PHD2{:}O_2)/K_M(PHD2{:}O_2)$ estimates, and provides a framework for the understanding at the atomistic level of the oxygen-sensing properties of a prototype oxygenase.

Key-words: oxygen sensing; oxygenases; PHD; HIF; ABF; metadynamics

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