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Biomolecular Dynamics, Function, Visualization, and the Energy Landscape

Since the landmark report by McCammon, Gelin and Karplus in 1977, molecular dynamics and Monte Carlo simulations of proteins are now widely used as tools to investigate biomolecular structure and dynamics, ranging from studies of ligand binding and enzyme-reaction mechanisms to problems of denaturation and protein folding. Fundamental to such simulations is the classical representation of the energy (potential energy functions yielding a force field) of the protein as a function of its atomic coordinates – not its electron coordinates (wave function theory) or density (density functional theory). A classical description ignores the explicit presence electrons and describes the time-evolution of the nuclear positions alone, where $\mathcal{O}(n^2), n =$ number of atoms. Consequently, simulations of a million atoms have been reported. Classical descriptions work well when the Born-Oppenheimer approximation is valid, the electronic structure is not of interest, the temperature is modest (not too low), and there is no bond breaking or forming. The seminar will conclude discussing how molecular dynamics to sample conformational space and multivariate analysis was used to aid in the structural, dynamic, and electronic origin of the spectroscopically observed carbonmonoxy myoglobin (MbCO) A states. Ten short (400 ps) and two longer time (1.2 ns) molecular dynamics simulations, starting from five different crystallographic and solution phase structures centered in a 37 Å radius sphere of water, were used to sample the native-fold of MbCO. Three discrete conformational substates resulted where the primary structural differences corresponded to a variable strength nonbond interaction between His64, Arg45, and the bound ligand. The A_0 state (*out* conformation) was determined to have both Arg45 and His64 removed from the heme pocket with negligible electrostatic effect on the ligand. Alternatively, His64 was determined to induce the redshifted frequencies characteristic of the A states ($A_{1\text{-}3}$) by forming a weak hydrogen bond between its protonated N_δ and the ligand (in/N_δ conformation). The $A_{1,2}$ state was specifically assigned to the in/N_δ conformation with Arg45 removed from His64 $\left(\Delta\nu_{comp} = -10.0 \pm 1.8\ cm^{-1}\right)$. The second and faster translational motion engaged Arg45 in an additional and cooperative electrostatic interaction with His64 that distinguished between the $A_{1,2}$ and A_3 states. The strongest red-shifted ligand stretch frequency (A_3 state) was computed when Arg45 interacted with His64 in the in/N_δ conformation. The polarizing effect of the distal histidine on the CO ligand $\left(\Delta\nu_{comp} = -19.0 \pm 6.8\ cm^{-1}\right)$ was increased by the positive charge on Arg45. Consequently, a new A-state model, which rationalizes the A_3 state based upon the fluctuating electrostatic field generated by the gate-like dynamics of His64 and Arg45, is presented, which is consistent with previously reported time scales for substate interconversion.