Supporting information:

Metadynamics in Essential Coordinates: Free Energy Simulation of Conformational Changes

Vojtěch Spiwok, Petra Lipovová, Blanka Králová

Contents:

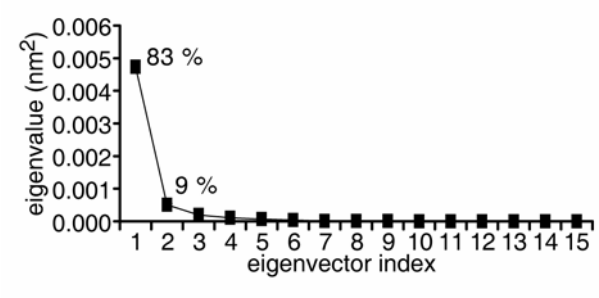

Figure S1. Eigenvalue plot (eigenvalue as a function of eigenvector index). This plot illustrates that the two most intensive collective motions account for the majority of overall motions of atoms selected for essential dynamics analysis (92 % of the sum of eigenvalues).

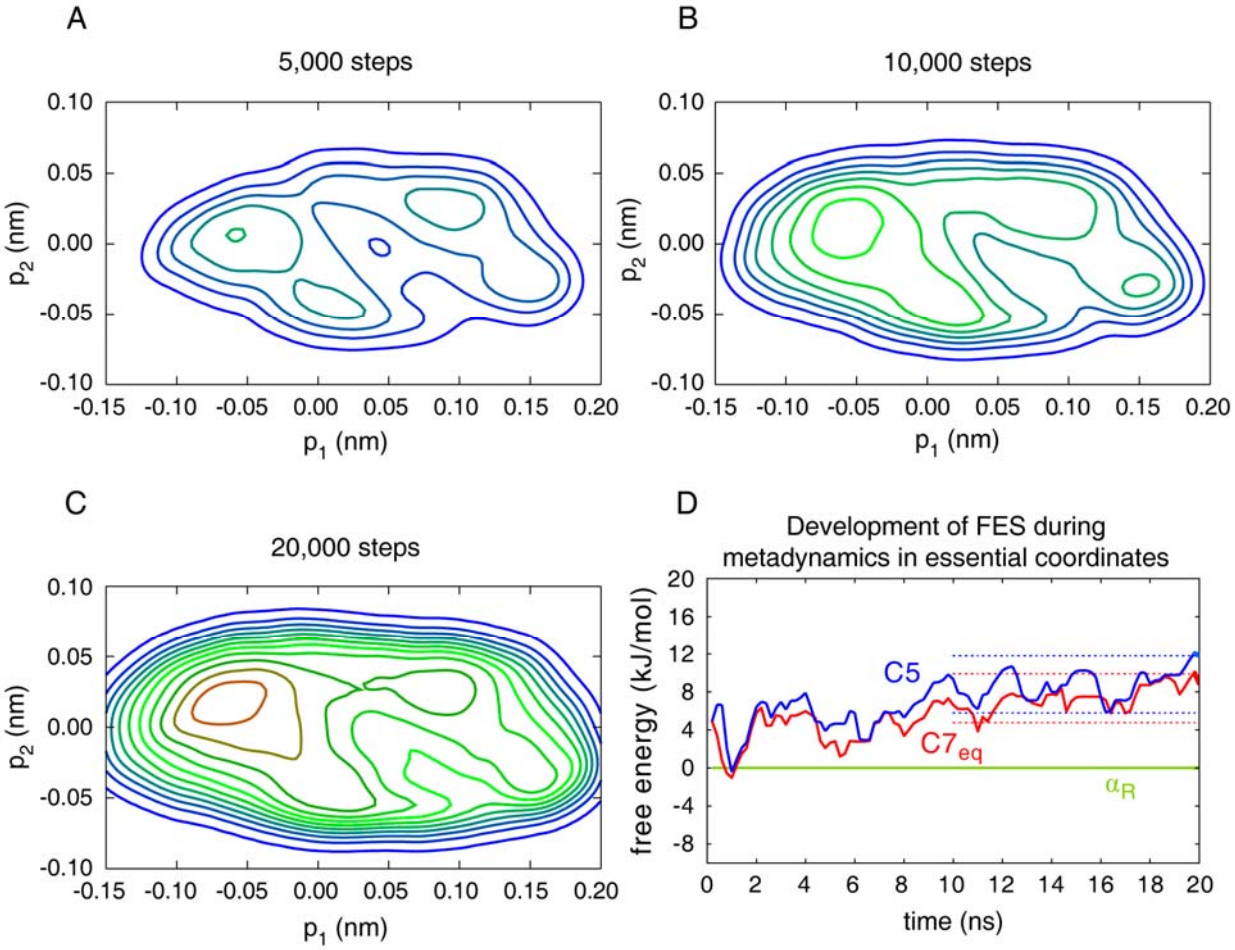

Figure S2: Development of the free energy surface as a function of essential coordinates during metadynamics in essential coordinates (starting from the α_R conformation). The free energy surface is illustrated after 5,000 (**A**), 10,000 (**B**) and 20,000 (**C**) steps. Contours are plotted every 4 kJ/mol. One step corresponds to 1.0 ps of classical MDS (1.2 ps including equilibration phase). Local minima corresponding to α_R, $C7_{eq}$ and C5 states were localized every 200 steps using a simple grid-based minima finder. Calculated values as a function of time are illustrated (**D**). Last 10,000 steps were used for calculation of average values and confidence intervals.

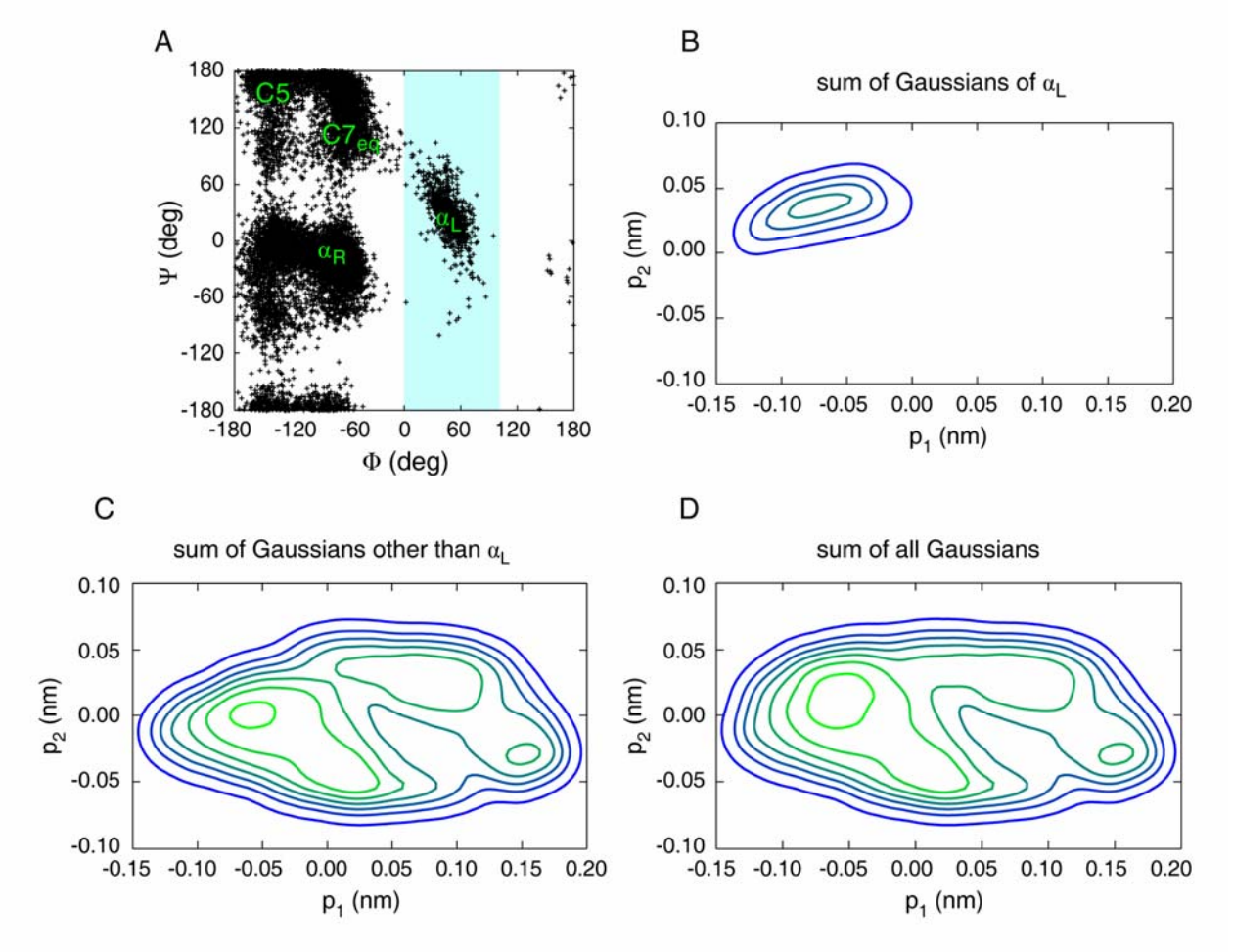

Figure S3: This figure addresses the problem of sampling the α_L conformation. Essential coordinates of this conformation were overlying those of the α_R conformation. In order to assess the effect of sampling of the α_L conformation, dihedral angles Φ and Ψ were calculated for initial coordinates of the first 10,000 steps of metadynamics (**A**). Steps with values 0 deg < Φ < 100 deg are located on the blue background. Sum of Gaussians corresponding to these steps is illustrated (**B**). Comparison of the free energy surface from which these Gaussians were subtracted (**C**) with the original free energy surface (**D**) indicates that an effect of sampling of α_L conformation on free energy values is small (approx. 1.2 kJ/mol for α_R). Contours are plotted every 4 kJ/mol.

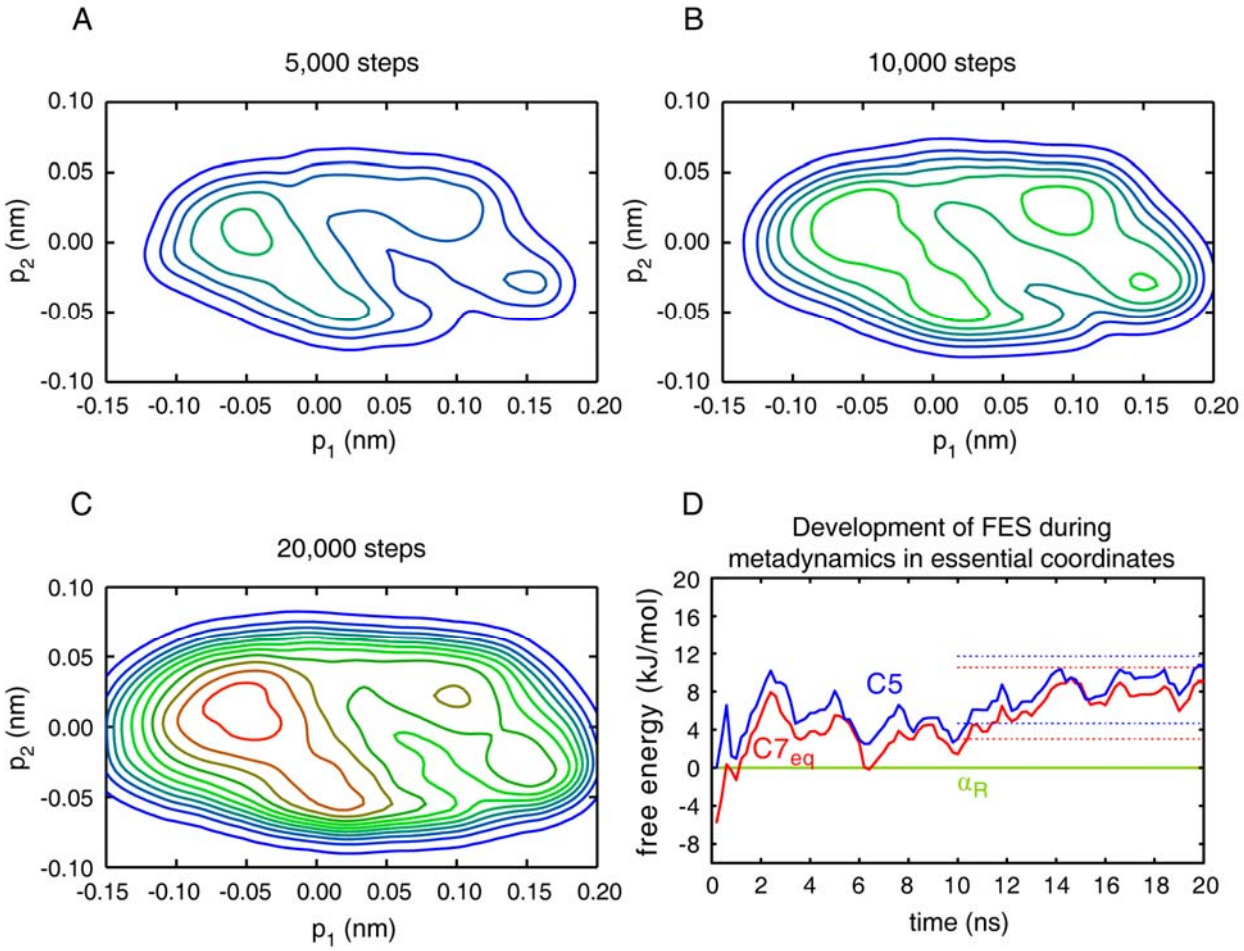

Figure S4: Accuracy of metadynamics in essential coordinates could be assessed by comparing it to another metadynamics run starting from a different initial state. The free energy surface, calculated by metadynamics in essential coordinates starting from $C7_{eq}$/C5 conformation, is illustrated after 5,000 (**A**), 10,000 (**B**) and 20,000 (**C**) steps. Contours are plotted every 4 kJ/mol. Local minima corresponding to α_R, $C7_{eq}$ and C5 states were localized as described in the caption of Figure S2 and their free energies as a function of time are illustrated (**D**).

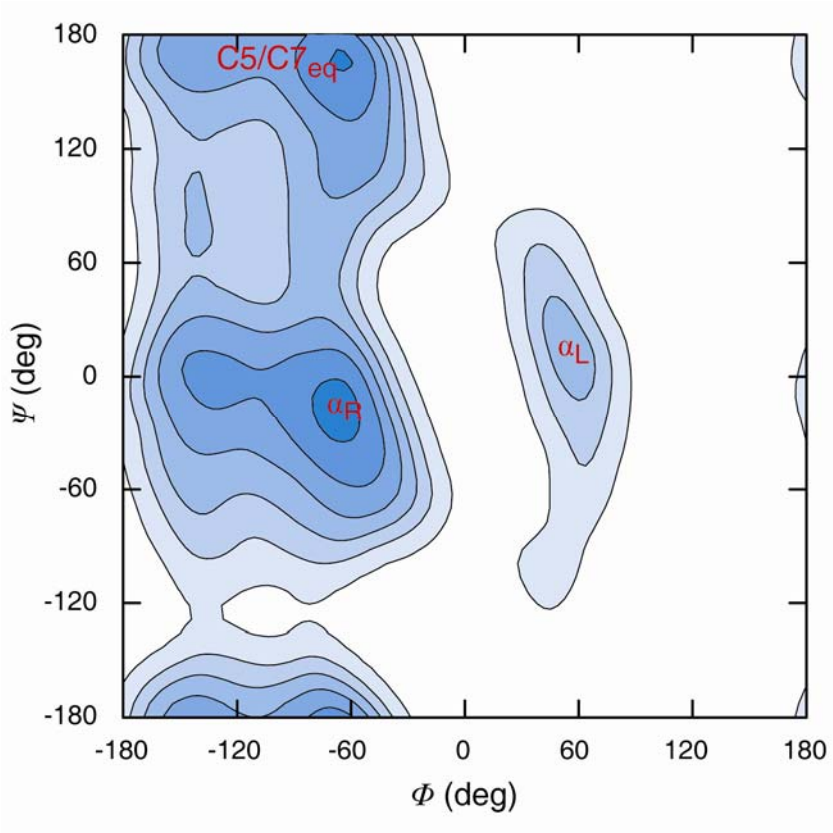

Figure S5: Accuracy of metadynamics in essential coordinates was also assessed by comparing it to metadynamics in the space of dihedrals Φ and Ψ. The free energy surface, calculated by metadynamics in dihedrals starting from α_R conformation is illustrated after 10,000 steps. Parameters used here were the same as in metadynamics in essential coordinates (w = 0.1 kJ/mol, microscopic MDS consisted of 0.2 ps of equilibration and 1.0 ps of sampling), except the parameter δp which was 10 deg. Local minima corresponding to α_R and $C5/C7_{eq}$ states were localized as described in the caption of Figure S2. Free energy of the state $C5/C7_{eq}$ was calculated as 5.6 ± 2.3 kJ/mol. States C5 and $C7_{eq}$ were not sufficiently resolved. Contours are plotted every 4 kJ/mol.