Funnel metadynamics on the Kelch domain of Keap1.

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Funnel metadynamics is a method that allows a ligand to enhance the sampling of the target binding sites and its solvated states. In this method, a funnel-shaped potential is applied to the system, reducing the space to explore in the unbound state. During the simulation, the system visits the bound and unbound states several times, allowing an accurate estimation of the binding free-energy surface within a reasonable simulation time [1]. In this work, we performed funnel metadynamics on a DLGex peptide and the Kelch domain of Keap1. The peptide contains the "DLG" motif necessary in Neh2 for Kelch binding. The Neh2 domain is an important transcription factor responsible for the cell's defense against oxidative stress. The initial structure for the peptide was taken from a 1 μs trajectory with the Amber99SB*-ILDNP force field, and the Kelch domain was retrieved from the Protein Data Bank.

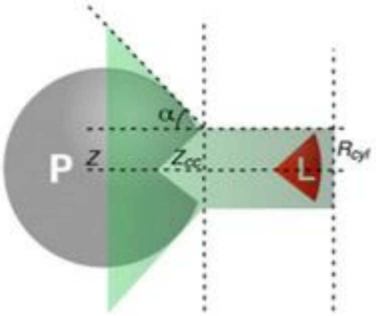

Figure 1: Schematic representation of the funnel restraint potential used in FM calculations. The shape of the funnel can be customized on the target by setting a few parameters. Given z, the axis defining the binding path of the ligand, z_{cc} is the distance at which the potential changes from a cone shape into a cylinder. The α angle defines the amplitude of the cone and R_{cyl} is the radius of the cylindrical section [1].

References

1. Limongelli, V., Bonomi, M. & Parrinello, M. Funnel metadynamics as accurate binding free-energy method. *Proc. Natl. Acad. Sci.* **110,** 6358–6363 (2013).