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SUPPLEMENTAL INFORMATION

DNA groove preference shift upon phosphorylation of a protamine-like cationic peptide

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S.1 Binding Free Energies using MMPBSA

The Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) approach computes the free energy for binding of the peptide (ligand) L and the DNA (receptor) R to form the DNA-peptide complex C as follows.

$$\Delta G_{bind} = G_C - G_R - G_L \tag{1}$$

where G_L stands for free energy of ligand, G_R for free energy of receptor and G_C for free energy of complex.

ΔG_{bind} can be expressed as:

$$\Delta G_{bind} = \Delta E_{MM} + \Delta G_{sol} - T\Delta S = \Delta H - T\Delta S \tag{2}$$

where ΔE_{MM}, represents the change in the gas-phase molecular mechanics (MM) energy. The ΔE_{MM} term includes the changes in the vdW energies ΔE_{vdW}, electrostatic energies ΔE_{ele}, and internal energies ΔE_{int} (bond, angle, and dihedral energies). It is given by:

$$\Delta E_{MM} = \Delta E_{ele} + \Delta E_{vdW} + \Delta E_{int} \approx \Delta E_{ele} + \Delta E_{vdW} \tag{3}$$

ΔG_{sol} represents the change in solvation free energy. The ΔG_{sol} term includes the electrostatic solvation energy term ΔG_{PB} that arises from polar contribution and the nonpolar contribution term ΔG_{SA} between the solute and the continuum solvent. The polar contribution term is determined using Poisson-Boltzmann (PB) models, while the nonpolar energy is usually calculated using the solvent-accessible surface area (SASA). The ΔG_{sol} is written as

$$\Delta G_{sol} = \Delta G_{PB} + \Delta G_{SA} = \Delta G_{PB} + \Delta G_{npolar} + \Delta G_{disper} \tag{4}$$

where ΔG_{npolar} is the nonpolar contribution of repulsive solute-solvent interactions and ΔG_{disper} is the nonpolar contribution of attractive solute-solvent interactions to the solvation energy.

And, -$T\Delta S$ is the change in conformational entropy brought on by the ligand-receptor interaction. A sequence of conformational snapshots produced from MD simulations are typically used in normal-mode analysis to assess the change in conformational entropy, $T\Delta S$. In this study, we have used a two-phase thermodynamic (2PT) model rather than a normal-mode analysis to compute the change in conformational entropy due to computational efficiency and high accuracy. The 2PT model just needs one post-processing of the MD trajectory to calculate entropy. Since it doesn't require as many discrete MD simulations along the integration path as the traditional thermodynamic integration method, it is significantly more effective. The 2PT model calculates entropy based on the density of states (DoS) function.

Different energy terms computed from the MMPBSA method for the simulation systems in our work are tabulated below.

Energy Term	Systems			
(kcal/mol)	MAJ_NP	MIN_NP	MAJ_PH	MIN_PH
ΔE_{vdW} (a)	-54 ± 6	-72 ± 5	-34 ± 6	-42 ± 5
ΔE_{ele} (b)	-5816 ± 102	-5958 ± 82	-2238 ± 69	-2283 ± 54
ΔE_{MM} (a+b=c)	-5870 ± 104	-6030 ± 83	-2272 ± 70	-2325 ± 55
ΔG_{PB} (d)	5765 ± 99	5899 ± 78	2213 ± 66	2240 ± 50
ΔG_{npolar} (e)	-43 ± 3	-53 ± 2	-26 ± 4	-29 ± 2
ΔG_{disper} (f)	77 ± 4	91 ± 3	57 ± 7	75 ± 3
ΔG_{sol} (d+e+f=g)	5799 ± 101	5937 ± 78	2244 ± 66	2286 ± 50
ΔH (c+g=h)	-72 ± 10	-93 ± 9	-28 ± 10	-39 ± 8
$-T\Delta S^{\dagger}$ (i)	11 ± 4	13 ± 4	7 ± 2	8 ± 2
ΔG_{bind} (h+i)	**-60 ± 10**	**-79 ± 10**	**-21 ± 11**	**-31 ± 8**

†$T\Delta S$ is computed using 2PT model.

S.2 PMF plots for comparisons between phosphorylated and non-phosphorylated peptides' bindings affinities

Figure SF. 1 shows the binding free energy or PMF profiles F(ξ) generated from the US simulations. The binding distances ξ_{min} and binding affinities F(ξ_{min}) estimated for the four complexes are 6.4, 7.4, 8.0 and 10.3 Å and -86 ± 2, -44 ± 1, -27 ± 1 and -26 ± 1 kcal mol^{-1} for MIN_NP (blue), MAJ_NP (black), MIN_PH (yellow) and MAJ_PH (green), respectively. The binding of the native peptide is much stronger and tighter in the minor groove than in the major groove (-86 vs. -44 kcal mol^{-1} and 6.4 vs. 7.4 Å, blue vs. black). Phosphorylation of the peptide not only weakens the binding affinity but also removes the DNA groove preference (-27 vs. -26 kcal mol^{-1}, yellow vs. green). However, although the binding distance increases upon phosphorylation in both grooves, it is still significantly shorter in the minor groove than in the major groove (8.0 vs. 10.4 Å, yellow vs. green). That is, in the case of the phosphorylated peptide, the overall shape and the well depth of PMF are similar in both major and minor grooves, but the location of the PMF minimum is shifted. This peculiar binding characteristics of the phosphorylated peptide is probably due to a binding-induced permanent deformation of the minor groove (see Figure 7).

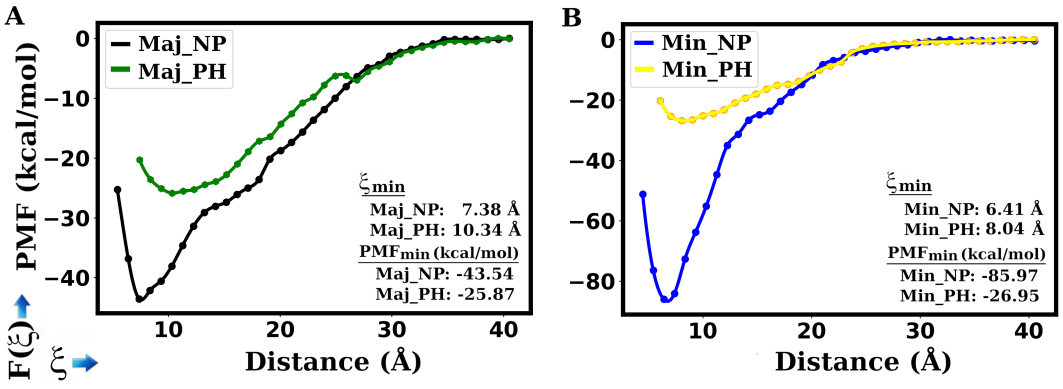

Figure SF. 1: Potential of mean force (PMF) F(ξ) profiles along the reaction coordinate (ξ) corresponding to pulling the peptide out of the major or minor groove in four DNA-peptide complexes, which present comparisons between bindings affinities of phosphorylated and non-phosphorylated peptides in major groove (A) and minor groove (B) of the DNA. The comparisons between bindings affinities to major and minor grooves are presented in Figure 6(A-B).