	ΔΔS	Hydrophobicity	HB(all)	HB(6)
R	0.43	0.11	0.03	0.42
P-value	0.00001	0.26	0.76	0.00001

Table 1: P-test for knowledge-based energy terms consdiered in SAMPDI approach.

Hydrophobicity of protein residues is calculated using the following empirical formula originally developed in our previous work (Petukh, et al., 2015).

$$Hydro = \ln[rSASA(i) \times H(i)] \quad (1)$$

,where rSASA(i) is the relative SASA of residue i calculated by the NACCESS software (S. Hubbard, 1993); H(i) indicate the hydrophobic(positive value) and hydrophilic (negative value) for residue i. H(i) for all types of residues are shown in the Table 2(Wimley and White, 1996). HB(all) indicates counting of the total number of the HBs for the entire structures while HB(6) only computes the number of HBs within 6 Å of the mutations occurring sites.

Residue	***A***	***C***	***D***	***E***	***F***	***G***	***H***	***I***	***K***	***L***
Rotamer	0.2	-0.2	1.2	1	-1.1	0	0.57	-0.3	1	-0.6
Residue	***M***	***N***	***P***	***Q***	***R***	***S***	***T***	***V***	***W***	***Y***
Rotamer	-0.2	0.4	0.5	0.6	0.8	0.1	0.1	0.1	-1.9	-0.9

Table 2. Hydrophobic(positive value) and hydrophilic (negative value)for all types of amino acids.

	Averaged weighting coefficients in 5-fold cross validation	**Standard Deviation of weighting coefficients in 5-fold cross validation**	**Weighting coefficients from MLR in the training**
Y-Intercept	0.46	0.075	0.445
NS	-0.0025	0.0015	-0.0012
VE	0.098	0.016	0.088
CE	0.074	0.017	0.078
PS	0.046	0.01	0.048
S	0.14	0.068	0.14
HB	-0.045	0.025	-0.043

Table 3: Average weighting coefficients and corresponding standard deviation in 5-fold cross validation for all the energy terms. The determined weighting coefficients from MLR was

also shown for the comparison.

Reference:

Petukh, M., Li, M. and Alexov, E. Predicting Binding Free Energy Change Caused by Point Mutations with Knowledge-Modified MM/PBSA Method. *PLoS Comput Biol* 2015;11(7):e1004276.

S. Hubbard, J.M.T. 'NACCESS', Computer Program. *Department of Biochemistry and Molecular Biology, University College London*. 1993.

Wimley, W.C. and White, S.H. Experimentally determined hydrophobicity scale for proteins at membrane interfaces. *Nature Structural Biology* 1996;3(10):842-848.