

Table 1. PSD-95-PDZ3: linear regression models

Model Comparison		Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
whole protein	ESM1v ~ $\Delta\Delta G_f$	1565	21,260				
whole protein	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	1564	18,199	1	3,061.20	263.07	< 2.2e-16 ***
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f$	1323	15,721				
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	1322	13,441	1	2279.3	224.18	< 2.2e-16 ***
orthosteric sites	ESM1v ~ $\Delta\Delta G_f$	240	1845				
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	239	1704.8	1	140.21	19.657	1.413e-05 ***

Table 2. GRB2-SH3: linear regression model

Model Comparison		Res.Df	RSS	Df	Sum of Sq	F	Pr(>F)
whole protein	ESM1v ~ $\Delta\Delta G_f$	754	7,968				
whole protein	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	753	5,795	1	2,173.30	282.41	< 2.2e-16 ***
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f$	583	3,265				
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	582	3,020	1	245.48	47.311	1.568e-11 ***
orthosteric sites	ESM1v ~ $\Delta\Delta G_f$	169	1864.3				
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b$	168	1343	1	521.27	65.205	1.245e-13 ***

Table 3. PSD-95-PDZ3: linear mixed models

Model Comparison		npar	AIC	BIC	logLik	-2logLik	Chisq	Df	Pr(>Chisq)
whole protein	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	7575.2	7596.6	-3783.6	7567.2			
whole protein	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	7409.7	7436.5	-3699.9	7399.7	167.48	1	< 2.2e-16 ***
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	6354.3	6375.1	-3173.2	6346.3			
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	6215.8	6241.7	-3102.9	6205.8	140.57	1	< 2.2e-16 ***
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	1175.3	1189.2	-583.64	1167.3			
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	1155.6	1173	-572.78	1145.6	21.705	1	3.179e-06 ***

Table 4. GRB2-SH3: linear mixed models

Model Comparison		npar	AIC	BIC	logLik	-2logLik	Chisq	Df	Pr(>Chisq)
whole protein	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	3339.9	3358.4	1666	3331.9			
whole protein	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	3304.1	3327.2	-1647	3294.1	37.858	1	7.609e-10 ***
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	2461.3	2478.8	-1226.7	2453.3			
non-orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	2434.5	2456.4	-1212.3	2424.5	28.795	1	8.047e-08 ***
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + (1 \text{pos})$	4	810.36	822.92	-401.18	802.36			
orthosteric sites	ESM1v ~ $\Delta\Delta G_f + \Delta\Delta G_b + (1 \text{pos})$	5	807.81	823.52	-398.91	797.81	4.5424	1	0.03307 *

