

| base mapped edges $\Delta\Delta G$ (N = 58) |       |                     |          | cdk2 mapped edges $\Delta\Delta G$ (N = 25) |      |                    |          | jnk1 mapped edges $\Delta\Delta G$ (N = 31) |       |                     |          | mcl1 mapped edges $\Delta\Delta G$ (N = 71) |       |                     |          | p38a mapped edges $\Delta\Delta G$ (N = 56) |       |                    |          | ptp1b mapped edges $\Delta\Delta G$ (N = 49) |      |                    |          | thrombin mapped edges $\Delta\Delta G$ (N = 16) |       |                     |          | tyk2 mapped edges $\Delta\Delta G$ (N = 24) |       |                    |          | all mapped edges $\Delta\Delta G$ (N = 330) |       |                     |          |
|---|-------|---------------------|----------|---|------|--------------------|----------|---|-------|---------------------|----------|---|-------|---------------------|----------|---|-------|--------------------|----------|--|------|--------------------|----------|---|-------|---------------------|----------|---|-------|--------------------|----------|---|-------|---------------------|----------|
| RMSE: FEP+                                  | 1.03  | [95%: 0.86, 1.19]   | kcal/mol | RMSE: FEP+                                  | 1.11 | [95%: 0.85, 1.36]  | kcal/mol | RMSE: FEP+                                  | 1.00  | [95%: 0.75, 1.28]   | kcal/mol | RMSE: FEP+                                  | 1.41  | [95%: 1.19, 1.62]   | kcal/mol | RMSE: FEP+                                  | 1.03  | [95%: 0.84, 1.20]  | kcal/mol | RMSE: FEP+                                   | 1.22 | [95%: 0.86, 1.55]  | kcal/mol | RMSE: FEP+                                      | 0.93  | [95%: 0.63, 1.21]   | kcal/mol | RMSE: FEP+                                  | 0.93  | [95%: 0.67, 1.15]  | kcal/mol | RMSE: FEP+                                  | 1.14  | [95%: 1.05, 1.24]   | kcal/mol |
| RMSE: AMBER TI                              | 1.47  | [95%: 1.24, 1.71]   | kcal/mol | RMSE: AMBER TI                              | 1.13 | [95%: 0.87, 1.39]  | kcal/mol | RMSE: AMBER TI                              | 1.45  | [95%: 1.02, 1.91]   | kcal/mol | RMSE: AMBER TI                              | 1.83  | [95%: 1.59, 2.10]   | kcal/mol | RMSE: AMBER TI                              | 1.56  | [95%: 1.26, 1.86]  | kcal/mol | RMSE: AMBER TI                               | 1.40 | [95%: 1.07, 1.75]  | kcal/mol | RMSE: AMBER TI                                  | 0.62  | [95%: 0.35, 0.87]   | kcal/mol | RMSE: AMBER TI                              | 1.27  | [95%: 0.99, 1.52]  | kcal/mol | RMSE: AMBER TI                              | 1.50  | [95%: 1.38, 1.62]   | kcal/mol |
| MUE : FEP+                                  | 0.84  | [95%: 0.69, 1.00]   | kcal/mol | MUE : FEP+                                  | 0.91 | [95%: 0.65, 1.15]  | kcal/mol | MUE : FEP+                                  | 0.78  | [95%: 0.58, 1.01]   | kcal/mol | MUE : FEP+                                  | 1.16  | [95%: 0.97, 1.33]   | kcal/mol | MUE : FEP+                                  | 0.80  | [95%: 0.65, 0.98]  | kcal/mol | MUE : FEP+                                   | 0.89 | [95%: 0.66, 1.14]  | kcal/mol | MUE : FEP+                                      | 0.76  | [95%: 0.52, 1.02]   | kcal/mol | MUE : FEP+                                  | 0.75  | [95%: 0.53, 0.99]  | kcal/mol | MUE : FEP+                                  | 0.90  | [95%: 0.82, 0.97]   | kcal/mol |
| MUE : AMBER TI                              | 1.20  | [95%: 0.97, 1.42]   | kcal/mol | MUE : AMBER TI                              | 0.97 | [95%: 0.76, 1.21]  | kcal/mol | MUE : AMBER TI                              | 1.07  | [95%: 0.74, 1.44]   | kcal/mol | MUE : AMBER TI                              | 1.52  | [95%: 1.29, 1.76]   | kcal/mol | MUE : AMBER TI                              | 1.20  | [95%: 0.95, 1.49]  | kcal/mol | MUE : AMBER TI                               | 1.06 | [95%: 0.81, 1.33]  | kcal/mol | MUE : AMBER TI                                  | 0.46  | [95%: 0.28, 0.70]   | kcal/mol | MUE : AMBER TI                              | 1.07  | [95%: 0.80, 1.36]  | kcal/mol | MUE : AMBER TI                              | 1.17  | [95%: 1.08, 1.27]   | kcal/mol |
| R2 : FEP+                                   | -0.53 | [95%: -1.64, 0.10]  | kcal/mol | R2 : FEP+                                   | 0.07 | [95%: -0.61, 0.32] | kcal/mol | R2 : FEP+                                   | -1.56 | [95%: -4.02, -0.41] | kcal/mol | R2 : FEP+                                   | -0.51 | [95%: -1.33, 0.03]  | kcal/mol | R2 : FEP+                                   | 0.29  | [95%: -0.12, 0.54] | kcal/mol | R2 : FEP+                                    | 0.37 | [95%: 0.12, 0.54]  | kcal/mol | R2 : FEP+                                       | -3.16 | [95%: -7.96, -0.87] | kcal/mol | R2 : FEP+                                   | 0.33  | [95%: -0.35, 0.59] | kcal/mol | R2 : FEP+                                   | -0.02 | [95%: -0.24, 0.15]  | kcal/mol |
| R2 : AMBER TI                               | -2.16 | [95%: -4.27, -1.01] | kcal/mol | R2 : AMBER TI                               | 0.05 | [95%: -1.18, 0.49] | kcal/mol | R2 : AMBER TI                               | -4.43 | [95%: -9.54, -1.65] | kcal/mol | R2 : AMBER TI                               | -1.55 | [95%: -2.87, -0.69] | kcal/mol | R2 : AMBER TI                               | -0.64 | [95%: -1.91, 0.07] | kcal/mol | R2 : AMBER TI                                | 0.17 | [95%: -0.33, 0.43] | kcal/mol | R2 : AMBER TI                                   | -0.89 | [95%: -4.31, 0.46]  | kcal/mol | R2 : AMBER TI                               | -0.24 | [95%: -1.45, 0.23] | kcal/mol | R2 : AMBER TI                               | -0.74 | [95%: -1.18, -0.41] | kcal/mol |
| rho : FEP+                                  | 0.61  | [95%: 0.45, 0.75]   | kcal/mol | rho : FEP+                                  | 0.39 | [95%: 0.15, 0.64]  | kcal/mol | rho : FEP+                                  | 0.59  | [95%: 0.29, 0.83]   | kcal/mol | rho : FEP+                                  | 0.51  | [95%: 0.34, 0.65]   | kcal/mol | rho : FEP+                                  | 0.79  | [95%: 0.67, 0.86]  | kcal/mol | rho : FEP+                                   | 0.66 | [95%: 0.54, 0.79]  | kcal/mol | rho : FEP+                                      | 0.42  | [95%: -0.09, 0.74]  | kcal/mol | rho : FEP+                                  | 0.70  | [95%: 0.50, 0.84]  | kcal/mol | rho : FEP+                                  | 0.60  | [95%: 0.53, 0.67]   | kcal/mol |
| rho : AMBER TI                              | 0.52  | [95%: 0.28, 0.70]   | kcal/mol | rho : AMBER TI                              | 0.59 | [95%: 0.36, 0.77]  | kcal/mol | rho : AMBER TI                              | 0.22  | [95%: -0.19, 0.62]  | kcal/mol | rho : AMBER TI                              | 0.40  | [95%: 0.20, 0.57]   | kcal/mol | rho : AMBER TI                              | 0.56  | [95%: 0.37, 0.71]  | kcal/mol | rho : AMBER TI                               | 0.59 | [95%: 0.43, 0.74]  | kcal/mol | rho : AMBER TI                                  | 0.71  | [95%: 0.42, 0.90]   | kcal/mol | rho : AMBER TI                              | 0.49  | [95%: 0.17, 0.77]  | kcal/mol | rho : AMBER TI                              | 0.48  | [95%: 0.40, 0.56]   | kcal/mol |

