

| base $\Delta\Delta G$ (N = 1260) | | | | cdk2 $\Delta\Delta G$ (N = 240) | | | | jnk1 $\Delta\Delta G$ (N = 420) | | | | mcl1 $\Delta\Delta G$ (N = 1722) | | | | p38a $\Delta\Delta G$ (N = 1122) | | | | ptplb $\Delta\Delta G$ (N = 506) | | | | thrombin $\Delta\Delta G$ (N = 110) | | | | tyk2 $\Delta\Delta G$ (N = 240) | | | | all all pairs $\Delta\Delta G$ (N = 5620) | | | |
|----------------------------------|-------|---------------------|----------|---------------------------------|------|-------------------|----------|---------------------------------|-------|---------------------|----------|----------------------------------|-------|---------------------|----------|----------------------------------|-------|---------------------|----------|----------------------------------|------|-------------------|----------|-------------------------------------|-------|--------------------|----------|---------------------------------|------|-------------------|----------|---|-------|---------------------|----------|
| RMSE: FEP+ | 1.22 | [95%: 1.17, 1.26] | kcal/mol | RMSE: FEP+ | 1.52 | [95%: 1.41, 1.63] | kcal/mol | RMSE: FEP+ | 1.65 | [95%: 1.56, 1.74] | kcal/mol | RMSE: FEP+ | 1.49 | [95%: 1.44, 1.54] | kcal/mol | RMSE: FEP+ | 1.39 | [95%: 1.34, 1.44] | kcal/mol | RMSE: FEP+ | 1.16 | [95%: 1.08, 1.24] | kcal/mol | RMSE: FEP+ | 0.80 | [95%: 0.70, 0.90] | kcal/mol | RMSE: FEP+ | 0.83 | [95%: 0.76, 0.91] | kcal/mol | RMSE: FEP+ | 1.37 | [95%: 1.34, 1.39] | kcal/mol |
| RMSE: AMBER TI | 1.90 | [95%: 1.81, 1.98] | kcal/mol | RMSE: AMBER TI | 1.58 | [95%: 1.45, 1.69] | kcal/mol | RMSE: AMBER TI | 1.63 | [95%: 1.52, 1.74] | kcal/mol | RMSE: AMBER TI | 2.11 | [95%: 2.05, 2.18] | kcal/mol | RMSE: AMBER TI | 2.33 | [95%: 2.23, 2.42] | kcal/mol | RMSE: AMBER TI | 1.46 | [95%: 1.36, 1.55] | kcal/mol | RMSE: AMBER TI | 0.75 | [95%: 0.64, 0.85] | kcal/mol | RMSE: AMBER TI | 1.65 | [95%: 1.52, 1.78] | kcal/mol | RMSE: AMBER TI | 1.97 | [95%: 1.93, 2.01] | kcal/mol |
| MUE : FEP+ | 0.98 | [95%: 0.94, 1.01] | kcal/mol | MUE : FEP+ | 1.25 | [95%: 1.15, 1.37] | kcal/mol | MUE : FEP+ | 1.36 | [95%: 1.27, 1.44] | kcal/mol | MUE : FEP+ | 1.20 | [95%: 1.16, 1.24] | kcal/mol | MUE : FEP+ | 1.12 | [95%: 1.08, 1.17] | kcal/mol | MUE : FEP+ | 0.91 | [95%: 0.85, 0.97] | kcal/mol | MUE : FEP+ | 0.64 | [95%: 0.56, 0.73] | kcal/mol | MUE : FEP+ | 0.65 | [95%: 0.59, 0.72] | kcal/mol | MUE : FEP+ | 1.09 | [95%: 1.06, 1.11] | kcal/mol |
| MUE : AMBER TI | 1.48 | [95%: 1.42, 1.55] | kcal/mol | MUE : AMBER TI | 1.32 | [95%: 1.21, 1.43] | kcal/mol | MUE : AMBER TI | 1.33 | [95%: 1.24, 1.42] | kcal/mol | MUE : AMBER TI | 1.68 | [95%: 1.62, 1.74] | kcal/mol | MUE : AMBER TI | 1.86 | [95%: 1.79, 1.94] | kcal/mol | MUE : AMBER TI | 1.14 | [95%: 1.06, 1.22] | kcal/mol | MUE : AMBER TI | 0.57 | [95%: 0.48, 0.66] | kcal/mol | MUE : AMBER TI | 1.35 | [95%: 1.23, 1.48] | kcal/mol | MUE : AMBER TI | 1.55 | [95%: 1.52, 1.58] | kcal/mol |
| R2 : FEP+ | -0.23 | [95%: -0.37, -0.10] | kcal/mol | R2 : FEP+ | 0.22 | [95%: 0.10, 0.32] | kcal/mol | R2 : FEP+ | -0.84 | [95%: -1.17, -0.58] | kcal/mol | R2 : FEP+ | 0.02 | [95%: -0.07, 0.10] | kcal/mol | R2 : FEP+ | 0.05 | [95%: -0.05, 0.14] | kcal/mol | R2 : FEP+ | 0.62 | [95%: 0.55, 0.67] | kcal/mol | R2 : FEP+ | -0.08 | [95%: -0.52, 0.23] | kcal/mol | R2 : FEP+ | 0.79 | [95%: 0.74, 0.84] | kcal/mol | R2 : FEP+ | 0.10 | [95%: 0.06, 0.15] | kcal/mol |
| R2 : AMBER TI | -1.98 | [95%: -2.36, -1.63] | kcal/mol | R2 : AMBER TI | 0.16 | [95%: 0.02, 0.26] | kcal/mol | R2 : AMBER TI | -0.80 | [95%: -1.15, -0.51] | kcal/mol | R2 : AMBER TI | -0.97 | [95%: -1.15, -0.81] | kcal/mol | R2 : AMBER TI | -1.66 | [95%: -1.98, -1.37] | kcal/mol | R2 : AMBER TI | 0.39 | [95%: 0.28, 0.48] | kcal/mol | R2 : AMBER TI | 0.04 | [95%: -0.34, 0.32] | kcal/mol | R2 : AMBER TI | 0.19 | [95%: 0.00, 0.33] | kcal/mol | R2 : AMBER TI | -0.87 | [95%: -0.97, -0.77] | kcal/mol |
| rho : FEP+ | 0.78 | [95%: 0.76, 0.80] | kcal/mol | rho : FEP+ | 0.48 | [95%: 0.38, 0.57] | kcal/mol | rho : FEP+ | 0.84 | [95%: 0.76, 0.87] | kcal/mol | rho : FEP+ | 0.77 | [95%: 0.76, 0.79] | kcal/mol | rho : FEP+ | 0.65 | [95%: 0.62, 0.68] | kcal/mol | rho : FEP+ | 0.80 | [95%: 0.77, 0.83] | kcal/mol | rho : FEP+ | 0.71 | [95%: 0.61, 0.79] | kcal/mol | rho : FEP+ | 0.89 | [95%: 0.87, 0.92] | kcal/mol | rho : FEP+ | 0.73 | [95%: 0.72, 0.74] | kcal/mol |
| rho : AMBER TI | 0.43 | [95%: 0.39, 0.48] | kcal/mol | rho : AMBER TI | 0.47 | [95%: 0.39, 0.55] | kcal/mol | rho : AMBER TI | 0.47 | [95%: 0.40, 0.54] | kcal/mol | rho : AMBER TI | 0.65 | [95%: 0.62, 0.68] | kcal/mol | rho : AMBER TI | 0.38 | [95%: 0.34, 0.43] | kcal/mol | rho : AMBER TI | 0.71 | [95%: 0.67, 0.75] | kcal/mol | rho : AMBER TI | 0.76 | [95%: 0.68, 0.82] | kcal/mol | rho : AMBER TI | 0.57 | [95%: 0.49, 0.65] | kcal/mol | rho : AMBER TI | 0.53 | [95%: 0.51, 0.55] | kcal/mol |

