Supporting Information

Is quantum mechanics necessary for predicting binding free energy?

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Contents of Supporting Information

1 Robustness upon choice of minimization protocol

Protocol	Nonbond ID	Minimization parameter ID	Leave-one-out cv q2	
			QMLIECE [a]	LIECE
1	1	1	0.55	0.30
2	3	1	0.59	0.32
3	4	2	0.53	0.06
4	5	2	0.51	0.06
5	2	1	0.46	0.12
6	5	1	0.57	0.39
7	3	3	0.48	0.31
8	3	4	0.46	0.31
9	3	5	0.45	0.32

Nonbond ID	CHARMM nonbond-specification [b]
1	NBONDS NBXMOD 5 GROUP SWITCH CDIE VDW VSWI EXTEND GRAD QUAD CUTNB 180 WMIN 1.5 EPS 1.0
2	NBONDS NBXMOD 5 ATOM SWITCH VATOM VSWITCHED CUTNB 15.0 CTONNB 11 CTOFNB 14 EPS 1.0 E14FAC 0.5 WMIN 1.5 CDIE
3	NBONDS NBXMOD 5 ATOM SWITCH VATOM VSWITCHED CUTNB 180 EPS 1.0 E14FAC 0.5 WMIN 1.5 CDIE
4	NBONDS ATOM FSHIFT CDIE VDW VSHIFT CUTNB 180 WMIN 1.5 EPS 1.0
5	NBONDS ATOM FSWITCH CDIE VDW VSHIFT CUTNB 180 WMIN 1.5 EPS 1.0

Minimization parameter ID	CHARMM minimization commands [c]
1	cons harm force 20 sele (type C*) end mini sd nstep 200 cons harm force 10 sele (type C*) end mini abnr nstep 200 cons harm force 8 sele (type C*) end mini abnr nstep 200 cons harm force 6 sele (type C*) end mini abnr nstep 200 cons harm force 4 sele (type C*) end mini abnr nstep 200 cons harm force 2 sele (type C*) end mini abnr nstep 200 cons harm force 1 sele (type C*) end mini abnr nstep 10000 tolgrd 0.01
2	cons harm force 20 sele (protein and (type C*) or (type O*) or (type N*)) end mini sd nstep 200 cons harm force 10 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 200 cons harm force 8 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 200 cons harm force 6 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 200 cons harm force 4 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 200 cons harm force 2 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 200 cons harm force 1 sele (protein and (type C*) or (type O*) or (type N*)) end mini abnr nstep 10000 tolgrd 0.01
3	cons harm force 20 sele (type C*) end mini sd nstep 200 cons harm force 10 sele (type C*) end mini abnr nstep 200 cons harm force 8 sele (type C*) end mini abnr nstep 200 cons harm force 6 sele (type C*) end mini abnr nstep 200 cons harm force 4 sele (type C*) end mini abnr nstep 200 cons harm force 2 sele (type C*) end mini abnr nstep 200 cons harm force 1.1 sele (type C*) end mini abnr nstep 10000 tolgrd 0.01
4	cons harm force 20 sele (type C*) end mini sd nstep 200 cons harm force 10 sele (type C*) end mini abnr nstep 200 cons harm force 8 sele (type C*) end mini abnr nstep 200 cons harm force 6 sele (type C*) end mini abnr nstep 200 cons harm force 4 sele (type C*) end mini abnr nstep 200 cons harm force 2 sele (type C*) end mini abnr nstep 200 cons harm force 1.2 sele (type C*) end mini abnr nstep 10000 tolgrd 0.01
5	cons harm force 20 sele (type C*) end mini sd nstep 200 cons harm force 10 sele (type C*) end mini abnr nstep 200 cons harm force 8 sele (type C*) end mini abnr nstep 200 cons harm force 6 sele (type C*) end mini abnr nstep 200 cons harm force 4 sele (type C*) end mini abnr nstep 200 cons harm force 2 sele (type C*) end mini abnr nstep 200 cons harm force 1.3 sele (type C*) end mini abnr nstep 10000 tolgrd 0.01

Table 1. Influence of minimization protocol on fitting results for 44 peptidic inhibitors of WNV PR. [a] These leave-one-out q^2 of QMLIECE were calculated using semiempirical Hamiltonian PM3. We finally chose RM1 Hamiltonian because we found that RM1 is more sophisticated than PM3, and could attain higher fitting qualities. [b] The explanation of charmm nonbond-specification can be found at http://www.charmm.org/html/documentation/c34b1/nbonds.html . [c] The explanation of charmm minimization commands can be found at http://www.charmm.org/html/documentation/c34b1/minimiz.html .

2 Three-parameter LIECE and QMLIECE models

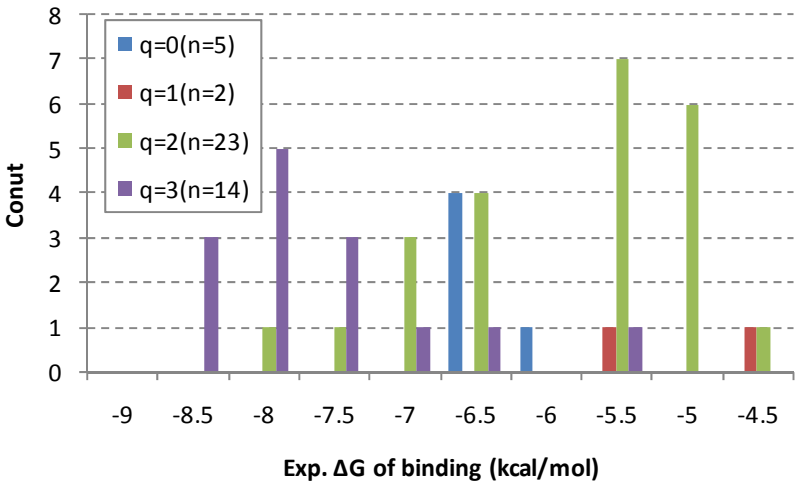
	α	β	$\Delta G_{tr,rot,bond}$ (kcal·mol^{-1})	Leave-one-out cross-valid rms error (kcal·mol^{-1})	q^2
WNV PR (44 peptidic inhibitors)					
$\alpha\Delta E_{vdW}+\beta\Delta G_{QM\_elesol}+\Delta G_{tr,rot,bond}$	0.036	0.026	-6.1	0.65	0.66
Standard deviation	±0.031	±0.005	±1.3		
$\alpha\Delta E_{vdW}+\beta\Delta G_{MM\_elesol}+\Delta G_{tr,rot,bond}$	*-0.012* [a]	0.030	-6.3	0.91	0.32
Standard deviation	*±0.029*	±0.008	±1.6		
CDK2 (73 non-peptidic inhibitors)					
$\alpha\Delta E_{vdW}+\beta\Delta G_{QM\_elesol}+\Delta G_{tr,rot}$	0.264	*-0.0015* [a]	1.0	0.97	0.79
Standard deviation	±0.026	±0.023	±0.6		
$\alpha\Delta E_{vdW}+\beta\Delta G_{MM\_elesol}+\Delta G_{tr,rot}$	0.283	0.023	0.9	0.96	0.79
Standard deviation	±0.021	±0.020	±0.6		

Table 2. Three-parameter LIECE and QMLIECE models. [a] Parameters with leave-one-out standard deviation larger than the average value are statistically not significant and are given in italics.

3 QMLIECE vs. simple models (WNV PR)

3.1 Histogram of ΔG_{bind} values

The 44 inhibitors can be separated according to number of positively charged groups as in the histograms enclosed. By inspection of the histograms one could speculate that the activity is related simply to the number of charges except for the compounds with q=2 (and q=1 which are only two) which seem shifted to less negative values.



3.2 Statistical tests

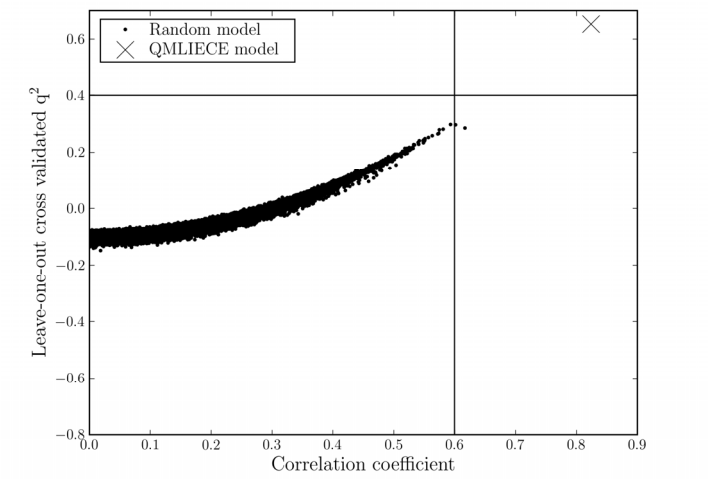
In response to an anonymous reviewer we compare the probability of chance correlation of QMLIECE and simple models derived using the total charge.
The QMLIECE model is the two-parameter model as in Equation (1) in the main text.
The LIECE and binary (LB) is a three-parameter model

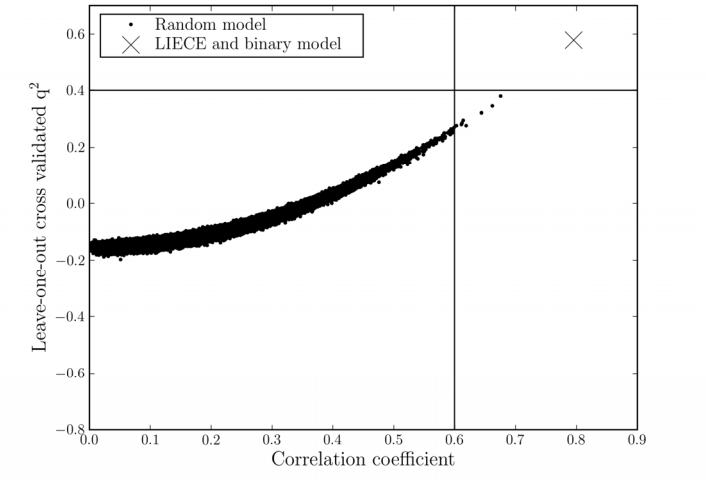
$$\Delta G_{bind} = 0.0318\Delta G_{MM\_elesol} + 1.1307Q_2 - 6.3154$$

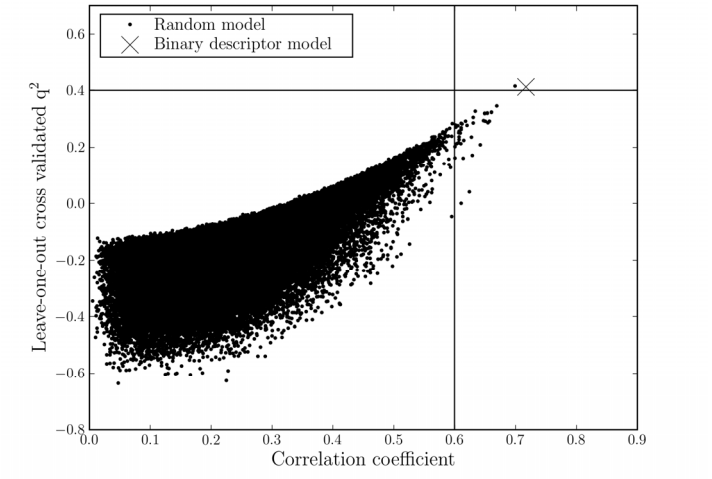
where ΔG_{MM_elesol} is the electrostatic contribution of binding free energy calculated by force field method, and Q_2 is a binary descriptor described below..
The binary descriptor (BD) is a five-parameter model

$$\Delta G_{bind} = 1.141Q_0 + 2.325Q_1 + 1.451Q_2 - 0.350Q_3 - 7.625$$

where "Q_n" is a binary descriptor, equals to one for ligands with charge of *n* and zero for all others.





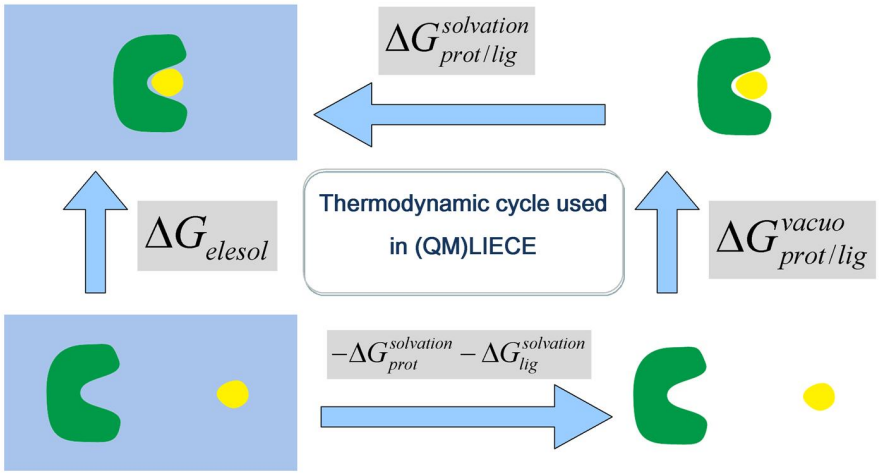


These statistical tests evaluate the predictive power of QMLIECE and two simple models. For each of the three models a total of 100000 models are generated by random guessing of the binding affinities (see main text for details).

The rationale behind this statistical test is that the significance of the model is low if there is a significant correlation between descriptors and randomized values of ΔG_{bind}. In other words, the

distance between the actual model (cross) and random models (dots) is an indicator of predictive power, i.e., lack of chance correlation. Note that the QMLIECE performs better in this test than LB, and much better than BD. This behavior is consistent with the decreasing physical soundness and increasing amount of fitting parameters in going from QMLIECE to LB and BD. The horizontal line at q^2=0.4 and the vertical line at R=0.6 are drawn to better compare the plots.

4 Thermodynamic cycle used in (QM)LIECE to calculate the binding free energy in solution



$$\Delta G_{elesol} = \Delta G^{vacuo}_{prot/lig} + \Delta G^{solvation}_{prot/lig} - \Delta G^{solvation}_{prot} - \Delta G^{solvation}_{lig}$$