# Necessity of quantum mechanics for predicting binding free energy

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## Introduction

We demonstrate the necessity of quantum mechanics (QM) for predicting binding free energy by comparing the results of the linear interaction energy model with continuum model (LIECE[1]) and the equivalent model with QM (QMLIECE). Three enzymes belonging to different classes are used. For the enzyme/inhibitor complexes dominated by variable charge-charge interactions (WNV NS3-NS2B protease), the application of QM is necessary. Molecule mechanics (MM) otherwise behaves with similar accuracy to QM for HIV-1 protease and cyclin-dependent kinase 2 (CDK2).

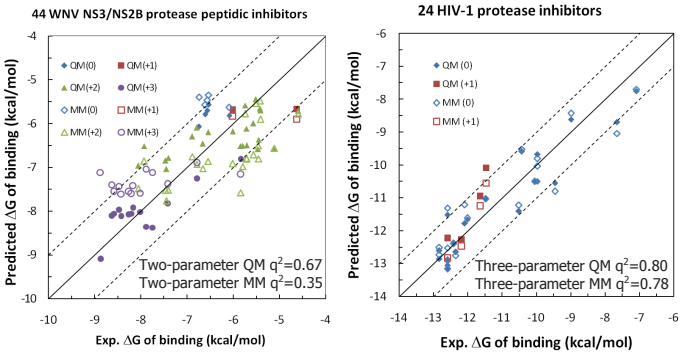
## Method

### Optimization

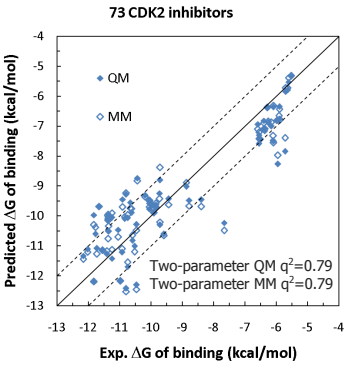
All the complexes are minimized by CHARMM and the CHARMm22 force field (Accelrys Inc.) with the partial charges derived from MPEOE approach.

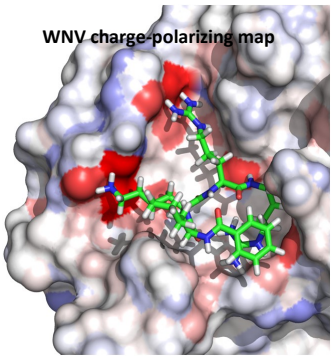
### Energy calculation

In LIECE, coulombic and van der Waals energies were calculated by CHARMm22, while in QMLIECE, vacuum interaction energies were calculated by MOPAC[2] with the semiempirical Hamiltonian RM1[3], using the divide and conquer algorithm[4]. The electrostatic solvation energy was calculated by the finite-difference Poisson approach using the PBEQ module in CHARMM for both LIECE and QMLIECE.




*The numbers in the parentheses indicate the net charges of the inhibitors.*




*The blue color on the surface denotes atomic partial charges that become more positive upon binding, while red color means more negative atomic charges upon binding, and white color indicates atomic charges which do not change upon binding.*

## Binding free energy

The equations used for the fitting are two-parameter models,

$\Delta G_{bind} = \alpha \Delta G_{elesol} + \Delta G_{tr,rot,bond}$ for WNV

$\Delta G_{bind} = \alpha \Delta G_{elesol} + \beta \Delta G_{vdW}$ for CDK2

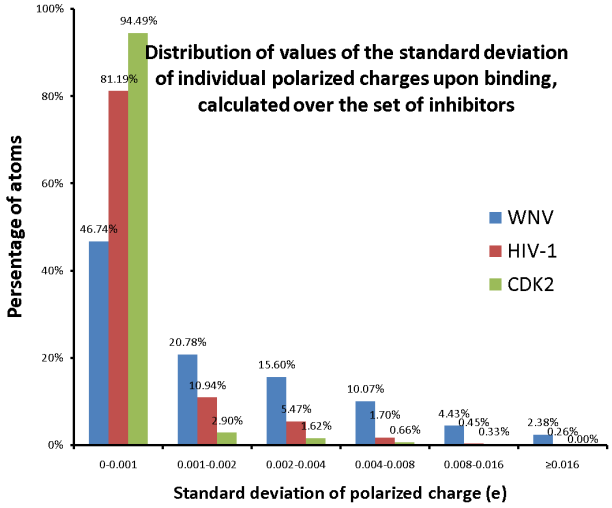
and a three-parameter model,

$\Delta G_{bind} = \alpha \Delta G_{elesol} + \beta \Delta G_{vdW} + \Delta G_{tr,rot,bond}$

where $\Delta G_{elesol}$ is the sum of the ligand/protein electrostatic interaction energy in solvent and the change in solvation energy of ligand and protein upon binding. For the vacuum interaction energy, QM and MM calculation are used in QMLIECE and LIECE, respectively. $\Delta G_{tr,rot,bond}$ accounts for the loss of translational and rotational degrees of freedom upon binding and the formation of a covalent bond for the 44 aldehyde inhibitors of WNV. $\Delta E_{vdW}$ is the ligand/protein van der Waals interaction energy.

## Results

For the prediction of relative binding affinities between protein and ligands, the necessity of QM depends on the variability of the polarized charge of each atom upon binding with different inhibitors. For the enzymes that have known inhibitors with a large variety of formal charges (e.g. from 0 to +3 in WNV), the use of electrostatic energy calculated by QM can significantly improve the predictive ability.




## References

[1] Huang, D.; Caflisch, A. *Journal of Medicinal Chemistry* **2004**, *47*, 5791-5797.
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[3] Rocha, G. B.; Freire, R. O.; Simas, A. M.; Stewart, J. J. P. *Journal of Computational Chemistry* **2006**, *27*, 1101-1111.
[4] Dixon, S. L.; Merz, K. M. *Journal of Chemical Physics* **1996**, *104*, 6643-6649.