Fujitsu *in-silico* Drug Discovery Technologies for creating active novel compounds.

MAPLE CAFEE: Accurate binding affinity prediction with massively parallel computation

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1. Introduction

Fast and reliable prediction of binding affinities for protein-ligand complexes is needed to find promising drug candidates from rationally designed compounds in *in-silico* drug discovery.

As the prediction of relative affinities among ligands for the identical receptor has shown successful results, we aim to develop a practical way to estimate the standard free energy of binding accurately with massively parallel computation.

(For technical details, see also the poster titled “A new practical approach to estimate the standard free energy of binding in bio-molecular system” by Y.Tanida et al.)

2. Methods and application examples

Our computation is based on the staged acceptance ratio (AR) method without any restraints to keep the ligand in the binding pocket.
Molecular dynamics(MD) simulation is performed with a modified version of GROMACS. RESP charges and modified GAFF parameters are assigned for both proteins and ligands with originally developed program, FF-FOM [1, 2].

Figure 1 shows a comparison between computation and experimental results for tRNA Ile Lysidine Synthetase(TilS) inhibitors. Results suggest that experimental values are relatively predictable within a range of experimental error, except a certain constant energy shift.

In addition to this, we also experienced to compute ligands for FKBP [2], RNA aptamer [3], PARP [4] and some other targets (unpublished yet), and obtained similar results.

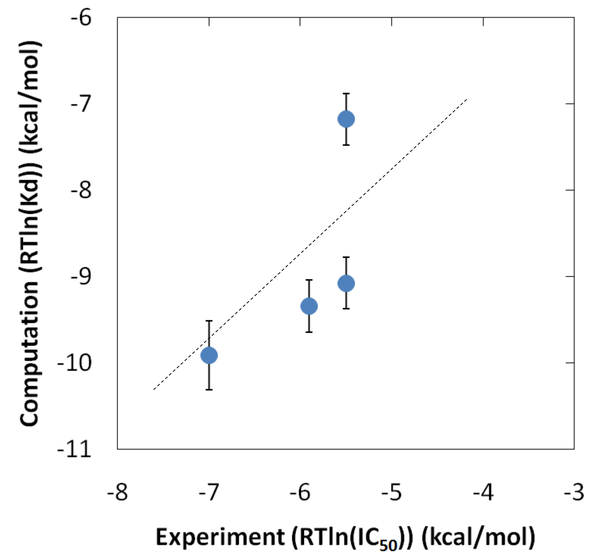

Figure 1 affinity prediction for TilS inhibitors.
The dashed line indicates RTln(IC_{50})-2.9

3. Long-time behavior for convergence and standard state correction

We studied the process which a ligand is decoupled from the surroundings to investigate a primary factor of the energy shift, using FK506/FKBP complex (PDB: 1FKF) as a typical example for validation.

(1) Long-time behavior of complex for convergence

Figure 3 shows free energy components for both a solvated ligand and a solvated complex in alchemical perturbation processes. The free energy change for complex gradually weakens and slowly converges with increasing simulation time. One of the reason for this behavior is considered to result from the difficulties of configurational sampling around λ∼0.825 as shown in section 4.

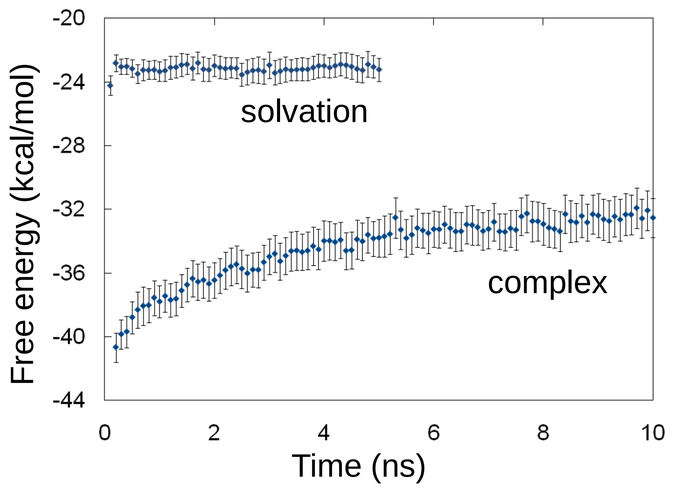

Figure 2 free energy components of FK506.

(2) Standard binding free energy

For direct comparison with experiments, a volume correction term $\Delta G_{vol.corr.} = -RT\ln(V/V_0)$ was added to take standard state into consideration, V and V_0 are the volume of simulation box and standard state, respectively.

$$\Delta G^0_{bind} = \Delta G_{complex} - \Delta G_{solv.} + \Delta G_{vol.corr.} \qquad (1)$$

The converged results are summarized in Table 1.

Table 1 Comparison of the computation and the experimental result. (unit : kcal/mol)

	$\Delta G_{complex}$	$\Delta G_{solv.}$	$\Delta G_{vol.corr.}$	ΔG^0_{bind}	$\Delta G^0_{expr.}$[5]
FK506	-32.4	-23.0	-2.9	**-12.3**	**-12.8**

4. Practical approach for estimation of standard binding affinities

In order to avoid sampling difficulties and reduce the computational costs, we tried the following attempts,

(1) Omission of direct sampling in intermediate states

Sampling inefficiency is occurred at around λ∼0.825 for vdW interaction (λ=0: fully bound, λ=1: decoupled) shown in Figure 3(B), because it takes a long time for the ligand to get out from the binding pocket and to wander in all possible configurational space.

(2) Interpolation between separated two phases

ΔG/Δλ (λ =[0.0, 0.825]) was taken from MD trajectories initially in bound state, ΔG/Δλ (λ =[0.85, 1]) was initially in unbound state. ΔG/Δλ is assumed to be smooth, and fitted with cubic spline functions as Figure 4(B).

Using the directly sampled data at around 7ns, ΔG/Δλ (λ= [0.825, 0.85]) was estimated and it gives $\Delta G_{complex}$ = -32.7(kcal/mol), which agrees well with the converged value at around 10ns in Table 1.

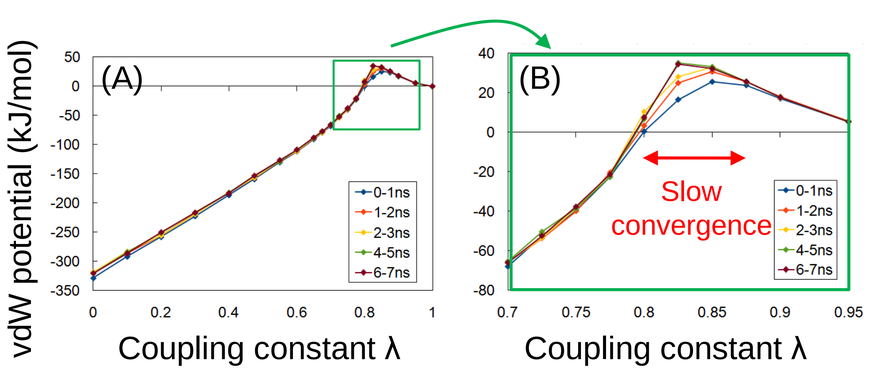

Figure 3 intermolecular van der Waals potential energy between FKBP and FK506 after discharged completely.

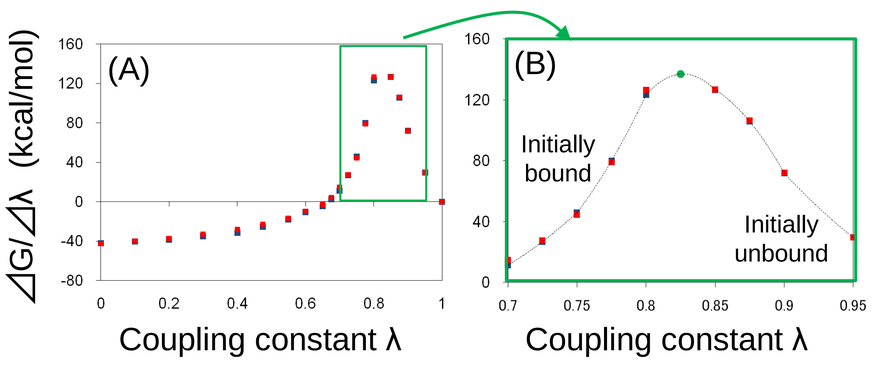

Figure 4 vdW component s of $\Delta G/\Delta\lambda$ for complex state.

5. Summary

Relative affinity prediction have given a good correlation with experiments for TilS inhibitors.

We further studied a long-time behavior for convergence in alchemical binding free energy computation for FK506/FKBP.

The standard free energy of binding showed a good agreement with the measured inhibition constant.

We also applied a new practical method to avoid sampling difficulties and found to be able to reproduce the equal value with less computational costs.

Acknowledgement

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