DIFFERENCE IN VIRTUAL SCREENING ENRICHMENT USING POLAR AND NON-POLAR INTERACTIONS OF MM-PB/GBSA METHODS

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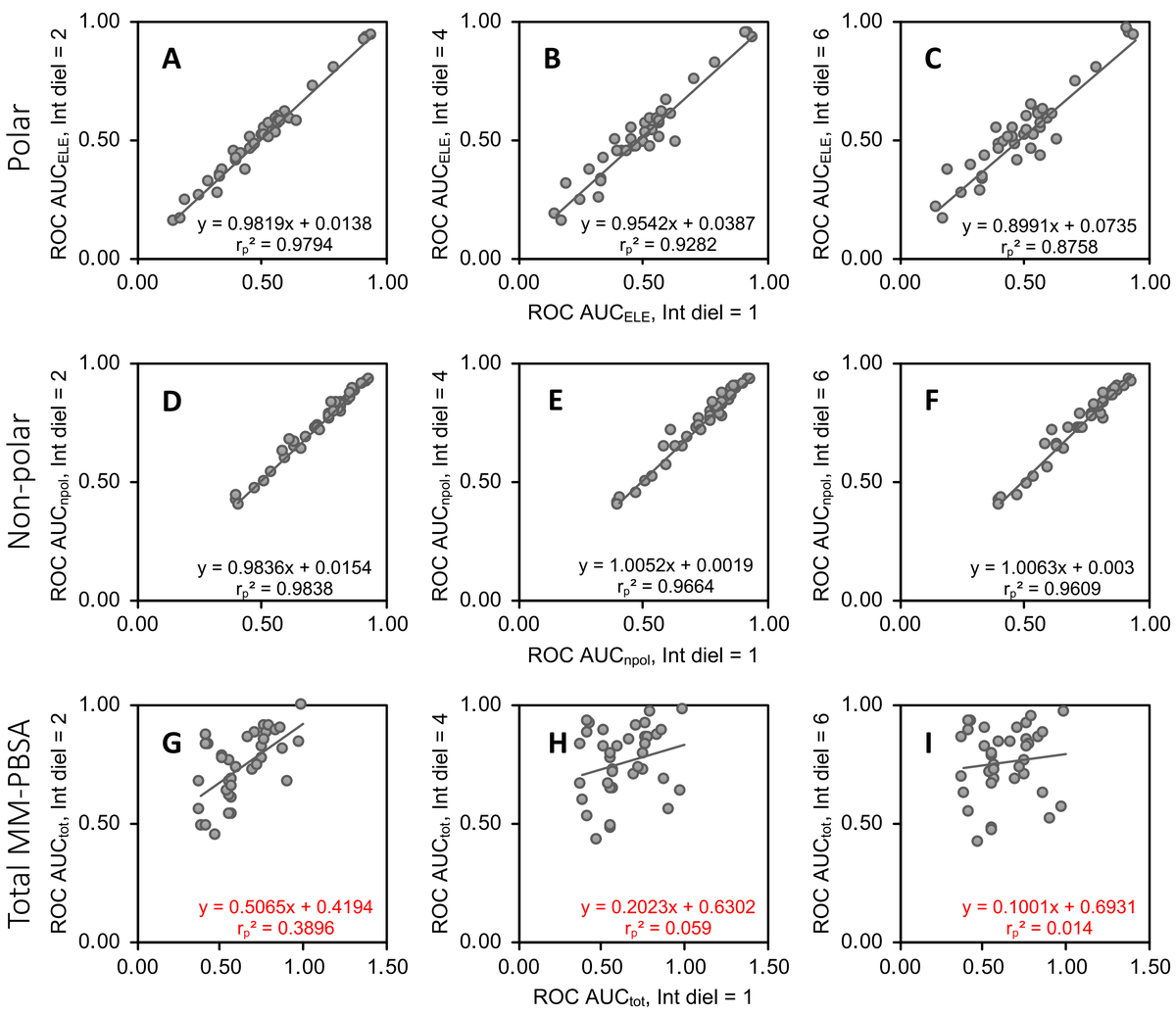
Introduction

MM-PB/GBSA free energy calculation has been suggested a better tool than most scoring functions. Both MM-PBSA and MM-GBSA binding energy calculation on docked poses yield moderate to good correlations to experimental data. Previous studies demonstrated that improvements in docking and virtual screening using MM-PB/GBSA methods were observed with increased internal dielectric value.[1,2] In our work, we assessed rescoring performance of MM-PB/GBSA methods on three test sets, each with the size of around 20 receptor proteins. We noticed no qualitative improvements in electrostatic estimation were observed by increasing the internal dielectric values for virtual screening. By using higher internal dielectrics, it quantitatively decreases the enrichment impairing effects from electrostatic and polar interactions to the total binding free energy prediction. Hence, future improvements in electrostatics can possibly improve the over all performance of MM-PB/GBSA calculations.

Docking & Virtual Screening: UNICON[3] was used to generate the top-scored tautomer and protonation states. PLANTS[4] was applied with $PLANTS_{chemplp}$ scoring function using a modified protocol.

MM-PBSA rescoring: MMPBSA.py included in AMBERTools15[5] is applied for MM-PBSA rescoring. The docked poses of ligands were minimised briefly before rescoring. Internal dielectric constants of 1, 2, 4, and 6 were tested.



Correlations of ROC AUC results between different internal dielectric constants

Table 1: ROC AUC correlation data for MM-GBSA energy compositions with different internal dielectrics (2, 4, and 6) to results using internal dielectric = 1. The AM1-BCC charging method was applied.

MM-GBSA energy compositions	Internal dielectric = 2			Internal dielectric = 4			Internal dielectric = 6		
	r_p^{2*}	m^{**}	b^{**}	r_p^{2*}	m^{**}	b^{**}	r_p^{2*}	m^{**}	b^{**}
Ele + polar solvation	0.9996	1.0019	0.0014	0.9951	1.0040	0.0011	0.9870	1.0154	0.0020
VDW + non-polar solvation	0.9981	1.0168	-0.0141	0.9924	1.0111	-0.0090	0.9857	1.0140	-0.0124
Total binding free energy	0.9061	0.8523	0.1214	0.3562	0.4572	0.4060	0.0685	0.2127	0.5775

* Pearson correlation coefficient squared

** m and b are the fitted parameter to a linear equation of the form $y = mx + b$

Table 2: ROC AUC correlation data for MM-PBSA energy compositions with different internal dielectrics (2, 4, and 6) to results using internal dielectric = 1. The Gasteiger charging method was applied.

MM-PBSA energy compositions	Internal dielectric = 2			Internal dielectric = 4			Internal dielectric = 6		
	r_p^{2*}	m^{**}	b^{**}	r_p^{2*}	m^{**}	b^{**}	r_p^{2*}	m^{**}	b^{**}
Ele + polar solvation	0.9870	0.9954	0.0180	0.9386	0.9598	0.0501	0.8742	0.9152	0.0769
VDW + non-polar solvation	0.9952	0.9982	-0.0033	0.9869	1.0098	-0.0078	0.9854	1.0194	-0.0114
Total binding free energy	0.3728	0.6109	0.3293	0.0628	0.2598	0.5636	0.0228	0.1595	0.6261

* Pearson correlation coefficient squared

** m and b are the fitted parameter to a linear equation of the form $y = mx + b$

Figure 1: ROC AUC correlation graphs of MM-PBSA decomposed energies with different internal dielectric values (2, 4, and 6) to results using internal dielectric = 1. The fitted linear equation and the squared Pearson correlation coefficients are as dieplayed. Worsened correlations were observed with total binding free energy predictions (**G - I**), but not when considering polar (**A - C**) or non-polar (**D – F**) energies alone.

Different distributions in KDE probability Density

13 out of 19 systems showed that increasing the internal dielectric values quantitatively decrease the deteriorating effects from electrostatic and polar energies on the overall binding free energy estimations.

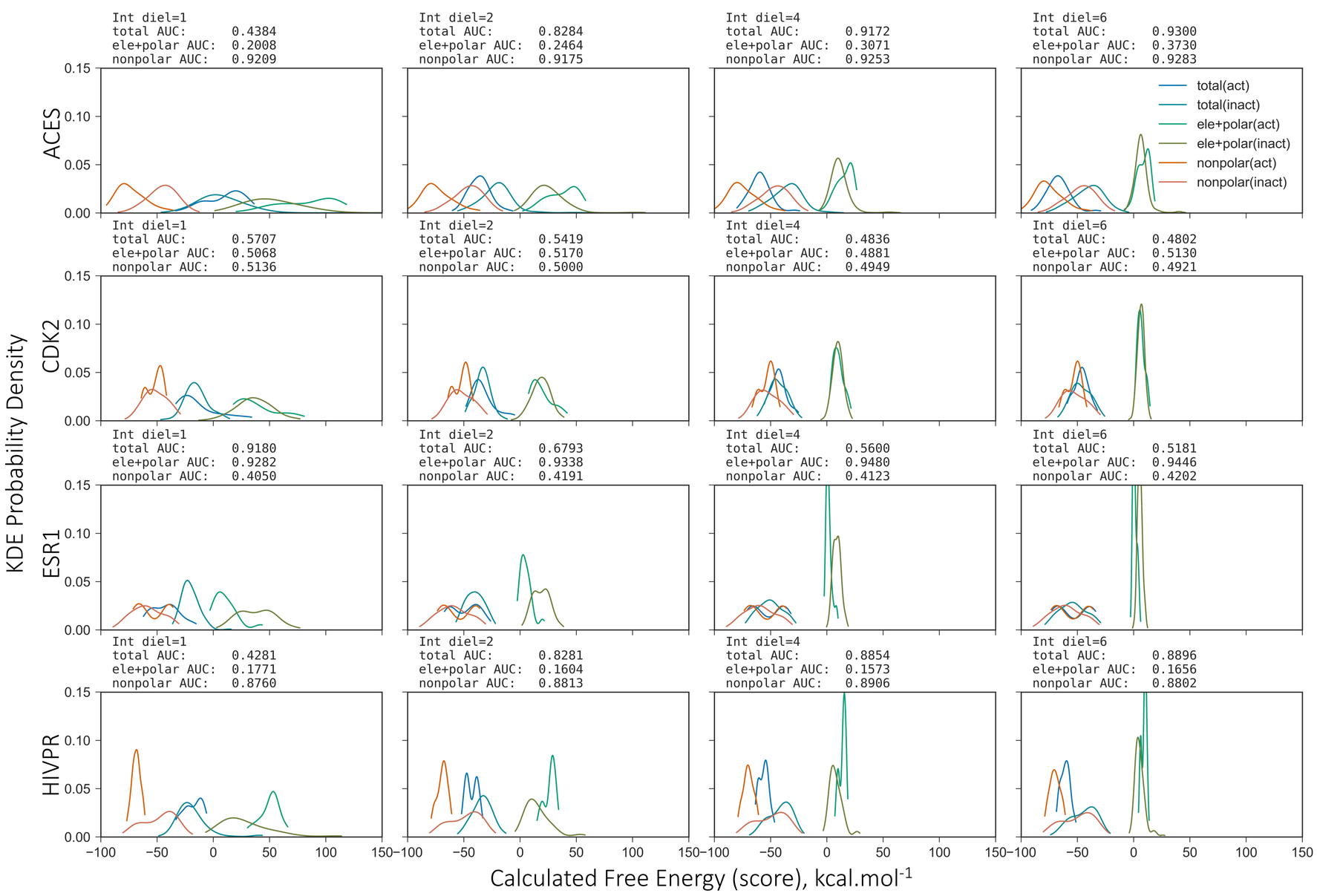


Figure 2: Examples of the KDE plots of actives and inactives of receptors within the test set. 13 out of 19 systems showed the distributions similar to those of **ACES** and **HIVPR** when increasing the internal dielectric values. Only 3 out of 19 were observed with the trends similar to **ESR1**.

Reference

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