This journal is © The Owner Societies 2013

Supporting Information

A Conformational Factorisation Approach for Estimating the Binding Free Energies of Macromolecules

K. Mochizuki, C.S. Whittleston, S. Somani, H. Kusumaatmaja and D.J. Wales

This journal is © The Owner Societies 2013

Residue name	Three letter code	$\theta_i^{\max}/2\pi$		
		$\alpha\beta$	$\beta\gamma$	$\gamma\delta$
Alanine	ALA	1.0	-	-
Arginine	ARG	0.2	0.3	0.5
Asparagine	ASN	0.5	1.0	-
Aspartic acid	ASP	0.5	1.0	-
Cysteine	CYS	1.0	-	-
Glutamic acid	GLU	0.3	0.5	1.0
Glutamine	GLN	0.3	0.5	1.0
Glycine	GLY	-	-	-
Histidine	HIS	0.3	0.5	-
Isoleucine	ILE	0.5	1.0	-
Leucine	LEU	0.5	1.0	-
Lysine	LYS	0.2	0.3	0.5
Methionine	MET	0.5	0.6	-
Phenylalanine	PHE	0.3	0.5	-
Proline	PRO	-	-	-
Serine	SER	1.0	-	-
Threonine	THR	1.0	-	-
Tryptophan	TRP	0.3	0.4	-
Tyrosine	TYR	0.3	0.5	-
Valine	VAL	1.0	-	-

TABLE S1: The maximum rotation amplitudes $\theta_i^{\max}$ for the amino acid side chain groups used in the current work. $\alpha\beta$, $\beta\gamma$ and $\gamma\delta$ refer to rotation about the C_α-C_β, C_β-C_γ and C_γ-C_δ bonds respectively.

PDB ID	C_α-RMSD from 2INE (Å)		Note
	All	in 16 Å from ligand	
2INE	0.000	0.000	Complexed with Phenylacetic Acid, RMSD reference
2IQ0	0.094	0.085	Complexed with Hexanoic Acid
2IS7	0.137	0.145	Complexed with Dichlorophenylacetic Acid
2INZ	0.155	0.134	Complexed with 2-Hydroxyphenylacetic Acid
1AH0	0.497	0.248	Pig aldose redectase complexed with Sorbinil
1EL3	0.301	0.156	Complexed with IDD384 inhibitor
1EKO	0.474	0.290	Pig aldose reductase complexed with IDD384 inhibitor
1IEI	0.723	0.609	Complexed with Zenarestat
1MAR	0.482	0.495	Complexed with Zopolrestat

TABLE S2: C_α - RMSD between 2INE which we used as "St-1" and 8 aldose reductase crystal structures with different ligands bound. C_α-RMSD for each pair is calculated for the whole system and the residues within 16 Å of the ligand, respectively.

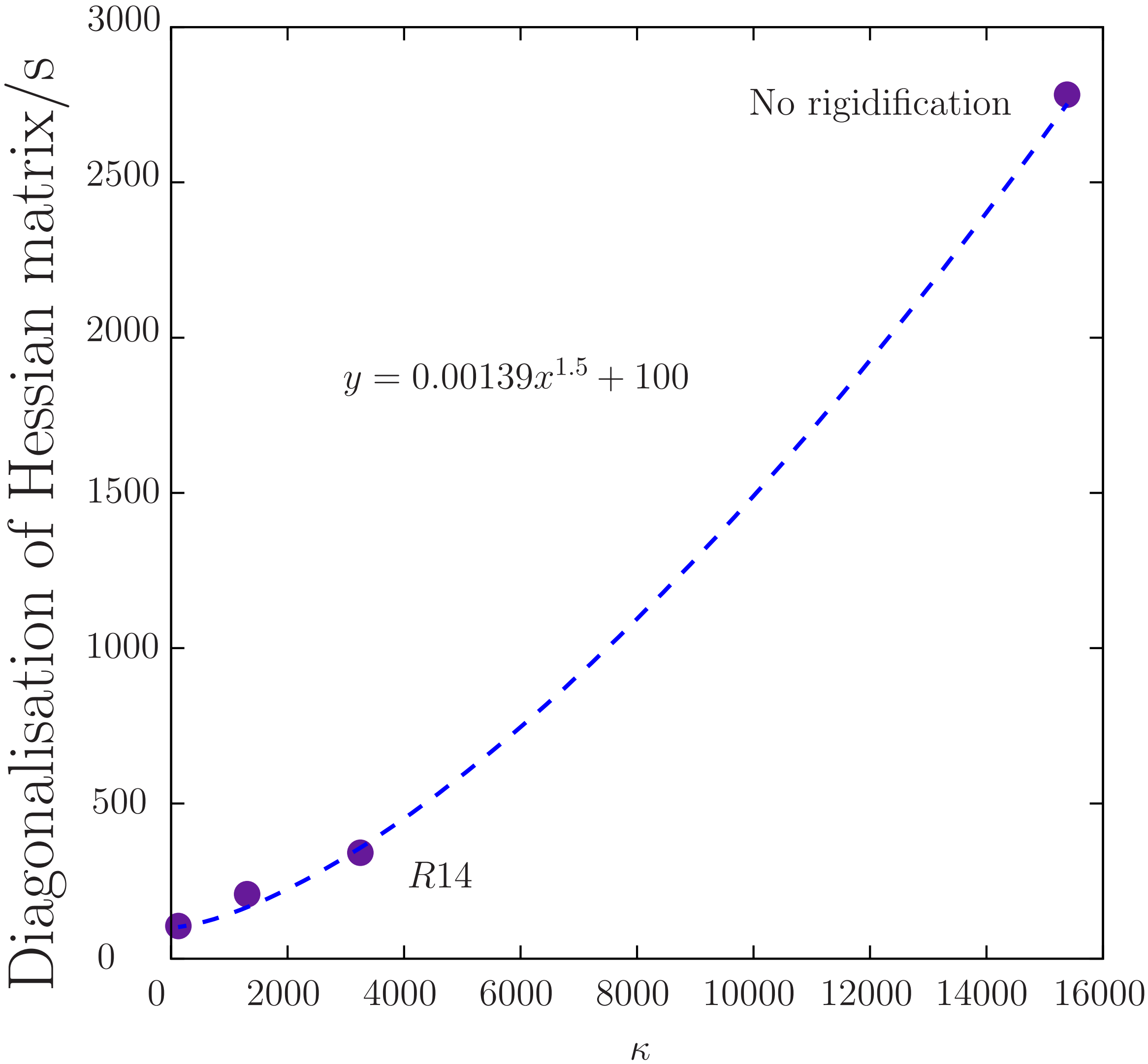

FIGURE S1: Average calculation time for diagonalisation of the Hessian matrix. $\kappa = 120$, 1299, 3246, corresponding to complexes with $R = 6$, 10, 14, and $\kappa = 15387$ (without any rigidification) are plotted. The fitting line scales as $\kappa^{1.5}$, described as blue dashed line. The calculations were performed on a 2.6GHz Xeon X5650 machine.

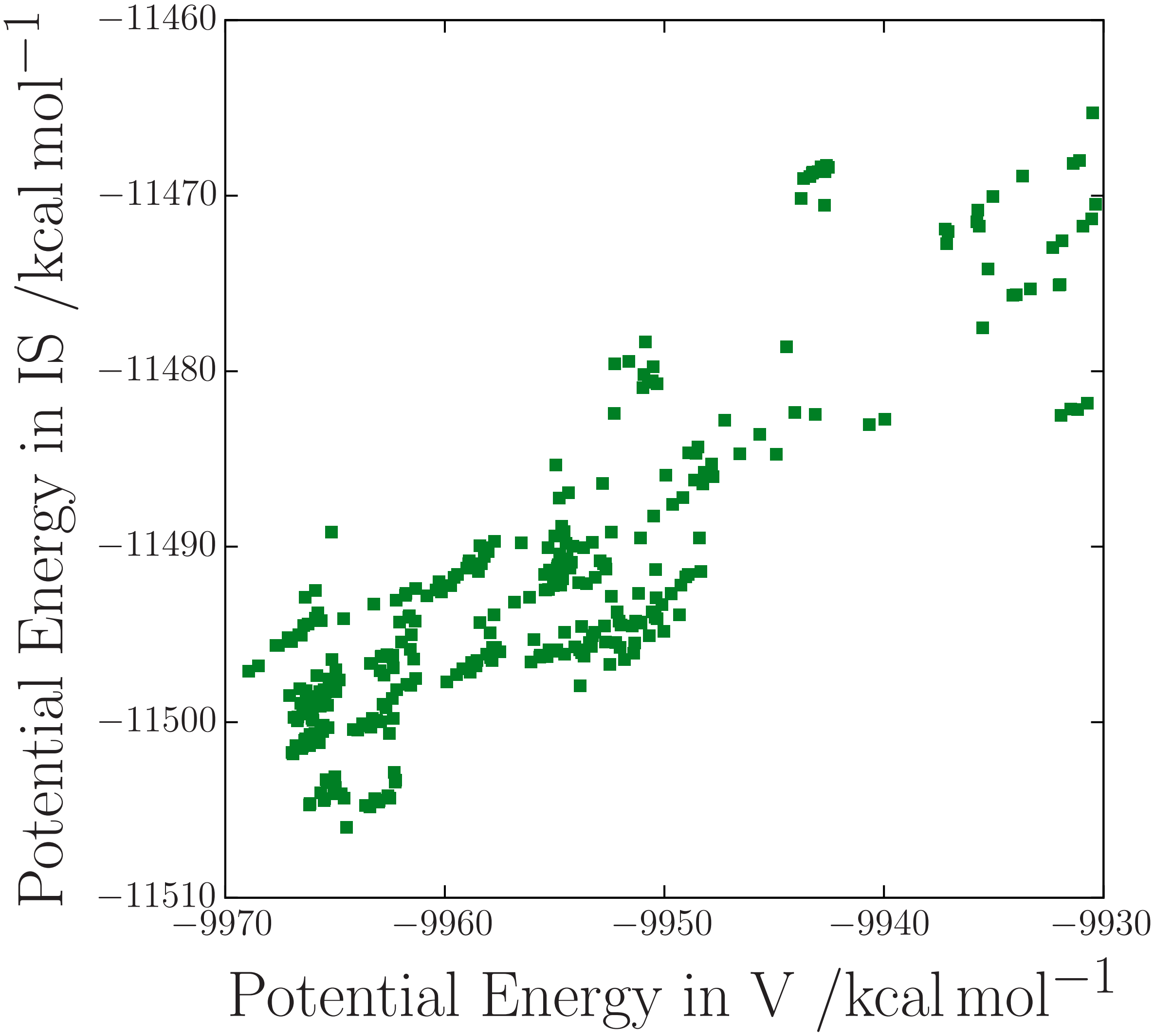

Figure S2: The potential energies in vacuum (V) and the corresponding recomputed energies in the implicit solvent (IS) are plotted. The Pearson correlation coefficient is 0.86.

Hessian in the local rigid body coordinates

In this section, we detail the derivations of the Hessian in the local rigid body coordinates. Our starting point is the first derivatives of the potential energy. For the translational degrees of freedom, $\mathbf{r}^I$, this is given by

$$\frac{\partial V}{\partial r^I_\alpha} = \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r^I_a(i)}\frac{\partial r^I_a(i)}{\partial r^I_\alpha} = \sum_{i\in I}\frac{\partial V}{\partial r^I_\alpha(i)}. \tag{1}$$

Additionally, the first derivative of the potential energy with respect to the rotational degrees of freedom, $\mathbf{p}^I$, gives

$$\frac{\partial V}{\partial p^I_\alpha} = \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r^I_a(i)}\frac{\partial r^I_a(i)}{\partial p^I_\alpha} = \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r^I_a(i)}\left[\frac{\partial \mathbf{S}^I}{\partial p^I_\alpha}\mathbf{x}^I(i)\right]_a. \tag{2}$$

We have employed the following relations in the above partial derivatives

$$\mathbf{r}^i = \mathbf{r}^I + \mathbf{S}^I\mathbf{x}^I(i); \quad i \in I, \tag{3}$$

$$\frac{\partial r^I_a(i)}{\partial r^I_\alpha} = \delta_{a\alpha}, \tag{4}$$

$$\frac{\partial r^I_a(i)}{\partial p^I_\alpha} = \left[\frac{\partial \mathbf{S}^I}{\partial p^I_\alpha}\mathbf{x}^I(i)\right]_a. \tag{5}$$

The second derivatives then follow in a similar manner. There are four separate cases to consider, and we derive them below for each case

$$\frac{\partial^2 V}{\partial r^I_\alpha \partial r^J_\beta} = \frac{\partial}{\partial r^I_\alpha}\left(\sum_{j\in J}\frac{\partial V}{\partial r^J_\beta(j)}\right) = \sum_{j\in J}\frac{\partial}{\partial r^J_\beta(j)}\left(\frac{\partial V}{\partial r^I_\alpha}\right) = \sum_{i\in I}\sum_{j\in J}\frac{\partial^2 V}{\partial r^I_\alpha(i)\partial r^J_\beta(j)}. \tag{6}$$

$$\begin{aligned}\frac{\partial^2 V}{\partial r^I_\alpha \partial p^J_\beta} &= \frac{\partial}{\partial r^I_\alpha}\left(\sum_{j\in J}\sum_{a=1}^{3}\frac{\partial V}{\partial r^J_a(j)}\left[\frac{\partial \mathbf{S}^J}{\partial p^J_\beta}\mathbf{x}^J(j)\right]_a\right)\\ &= \sum_{j\in J}\sum_{a=1}^{3}\frac{\partial}{\partial r^J_a(j)}\left(\frac{\partial V}{\partial r^I_\alpha}\right)\left[\frac{\partial \mathbf{S}^J}{\partial p^J_\beta}\mathbf{x}^J(j)\right]_a\\ &= \sum_{i\in I}\sum_{j\in J}\sum_{a=1}^{3}\frac{\partial^2 V}{\partial r^I_\alpha(i)\partial r^J_a(j)}\left[\frac{\partial \mathbf{S}^J}{\partial p^J_\beta}\mathbf{x}^J(j)\right]_a.\end{aligned} \tag{7}$$

This journal is © The Owner Societies 2013

$$
\begin{aligned}
\frac{\partial^2 V}{\partial p_\alpha^I \partial p_\beta^J} &= \frac{\partial}{\partial p_\alpha^I}\left(\sum_{j\in J}\sum_{a=1}^{3}\frac{\partial V}{\partial r_a^J(j)}\left[\frac{\partial \mathbf{S}^J}{\partial p_\beta^J}\mathbf{x}^J(j)\right]_a\right), \qquad \text{for } I \neq J \\
&= \sum_{j\in J}\sum_{a=1}^{3}\frac{\partial}{\partial r_a^J(j)}\left(\frac{\partial V}{\partial p_\alpha^I}\right)\left[\frac{\partial \mathbf{S}^J}{\partial p_\beta^J}\mathbf{x}^J(j)\right]_a \qquad (8) \\
&= \sum_{i\in I}\sum_{j\in J}\sum_{a=1}^{3}\sum_{b=1}^{3}\frac{\partial^2 V}{\partial r_b^I(i)\partial r_a^J(j)}\left[\frac{\partial \mathbf{S}^I}{\partial p_\alpha^I}\mathbf{x}^I(i)\right]_b\left[\frac{\partial \mathbf{S}^J}{\partial p_\beta^J}\mathbf{x}^J(j)\right]_a .
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial^2 V}{\partial p_\alpha^I \partial p_\beta^I} &= \frac{\partial}{\partial p_\alpha^I}\left(\sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r_a^I(i)}\left[\frac{\partial \mathbf{S}^I}{\partial p_\beta^I}\mathbf{x}^I(i)\right]_a\right) \\
&= \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial}{\partial r_a^I(i)}\left(\frac{\partial V}{\partial p_\alpha^I}\right)\left[\frac{\partial \mathbf{S}^I}{\partial p_\beta^I}\mathbf{x}^I(i)\right]_a + \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r_a^I(i)}\left[\frac{\partial}{\partial p_\alpha^I}\left(\frac{\partial \mathbf{S}^I}{\partial p_\beta^I}\right)\mathbf{x}^I(i)\right]_a \\
&= \sum_{i_1\in I}\sum_{i_2\in I}\sum_{a=1}^{3}\sum_{b=1}^{3}\frac{\partial^2 V}{\partial r_b^I(i_1)\partial r_a^I(i_2)}\left[\frac{\partial \mathbf{S}^I}{\partial p_\alpha^I}\mathbf{x}^I(i_1)\right]_b\left[\frac{\partial \mathbf{S}^I}{\partial p_\beta^I}\mathbf{x}^I(i_2)\right]_a \qquad (9) \\
&\quad + \sum_{i\in I}\sum_{a=1}^{3}\frac{\partial V}{\partial r_a^I(i)}\left[\frac{\partial^2 \mathbf{S}^I}{\partial p_\alpha^I \partial p_\beta^I}\mathbf{x}^I(i)\right]_a .
\end{aligned}
$$