

## Introduction

Molecular dynamics simulations of biomolecules are routinely performed in a water box with periodic boundary conditions. While the explicit representation of water molecules provides a high level of detail in regard to solute-solvent interactions, treating their degrees of freedom becomes gradually prohibitive with increasing system size. For systems whose detailed water interactions are not relevant to the properties under study, implicit solvation is a suitable method to represent the solvent-solute interactions [1, 4].

## SASA Model

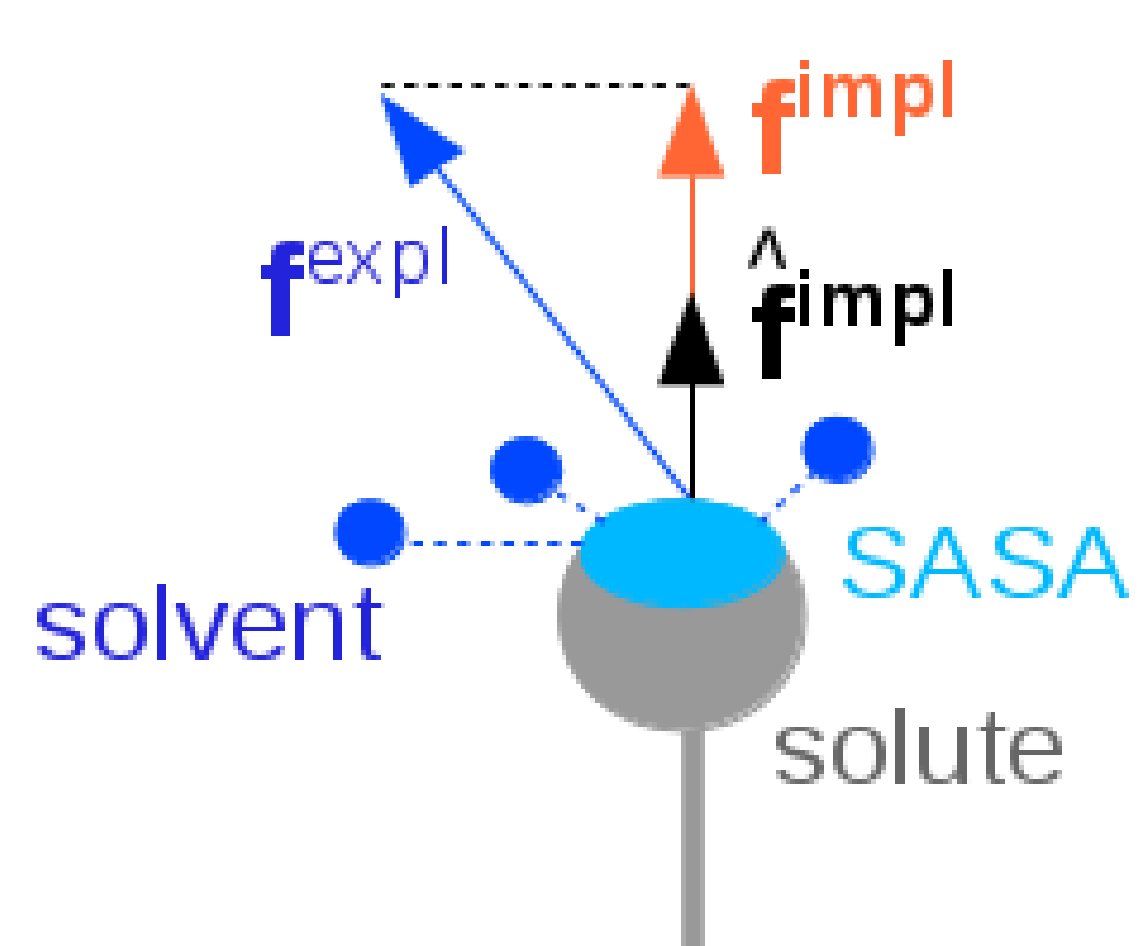
The interaction potential  $V^{impl}$  between the solvent and all solute atoms  $i$  can be assumed to be proportional to its solvent accessible surface area (SASA) [3], scaled by an atom-specific energy term  $\sigma_i^{SASA}$ :

$$V^{impl}(\mathbf{r}^N) = \sum_{i=1}^N \sigma_i^{SASA} A_i(\mathbf{r}^N). \quad (1)$$

The implicit solvent forces per atom are obtained from the derivative of the above equation with respect to  $\mathbf{r}_i$ :

$$\mathbf{f}_i^{impl} = -\sigma_i^{SASA} \frac{\partial A_i(\mathbf{r}^N)}{\partial \mathbf{r}_i}. \quad (2)$$

## Force Matching



$$|\mathbf{f}_i^{impl}| = \hat{\mathbf{f}}_i^{impl} \cdot \langle \mathbf{f}_i^{expl} \rangle \quad (3)$$

$$\sigma_i^{SASA} = -\frac{\frac{\partial A_i}{\partial \mathbf{r}_i}}{\left| \frac{\partial A_i}{\partial \mathbf{r}_i} \right|^2} \cdot \langle \mathbf{f}_i^{expl} \rangle \quad (4)$$

Fig. 1 : Force matching: Explicit solvent forces (blue arrow) exerted on the solute are projected on the normal of its SASA (black arrow), yielding the observed forces in explicit solvent with implicit solvent force (orange arrow). Eq. for Fig. 1 : Using the concept of force projection shown left, the expression for  $\sigma_i^{SASA}$  combines the observed forces in explicit solvent with the derivative of the atomic SASA.

## $\sigma_i^{SASA}$ Parameters

Using the solvation forces of 188 topologically diverse proteins in explicit and implicit solvent, a robust set of  $\sigma_i^{SASA}$  parameters was derived by force matching [2, 5]. Hydrophilic  $N$  and  $O$  atoms adopt negative  $\sigma_i^{SASA}$  parameters, those of hydrophobic  $C$  atoms are positive.

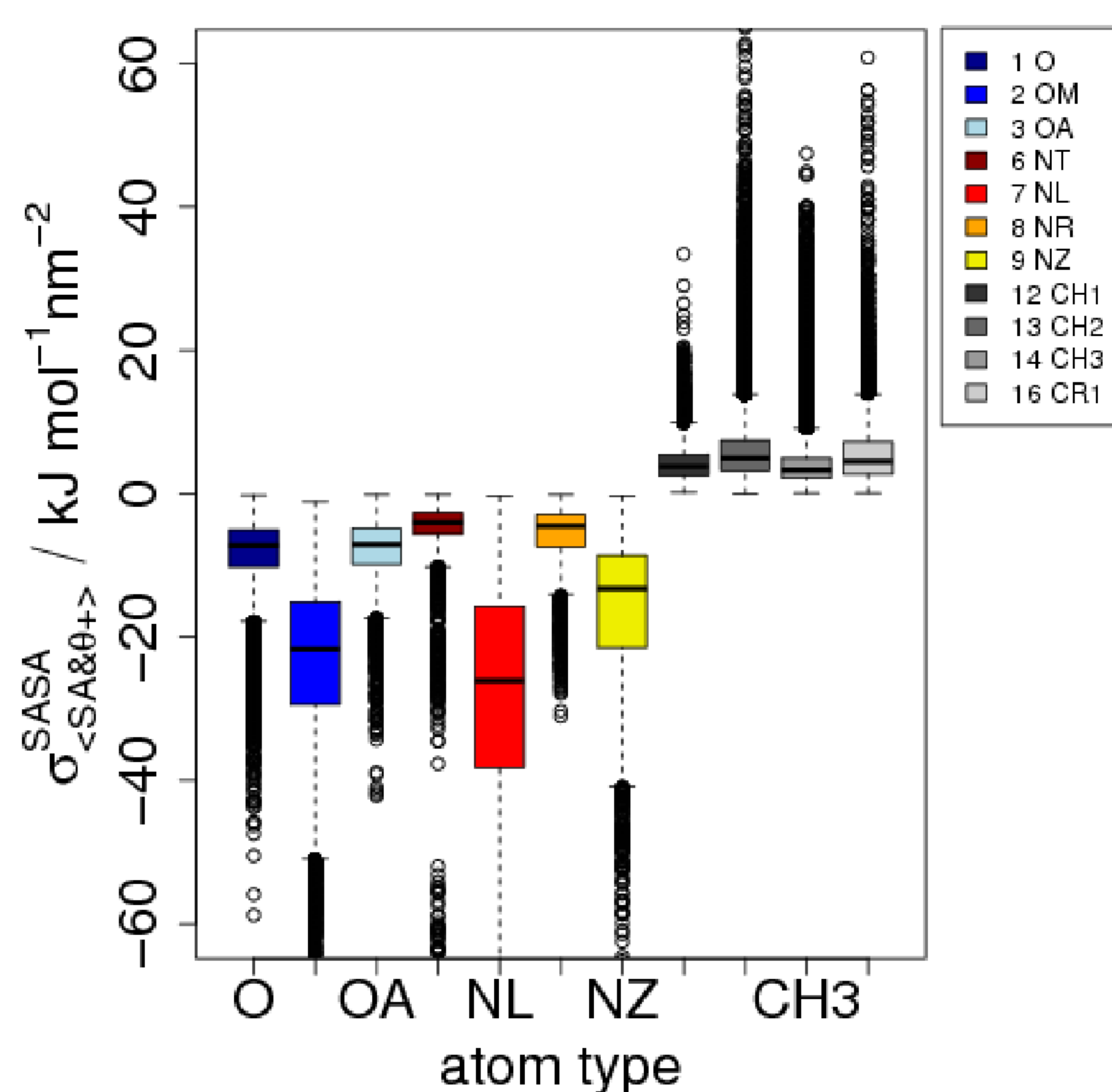


Fig. 2 :  $\sigma_i^{SASA}$  parameters derived by force matching.

## Friction Model

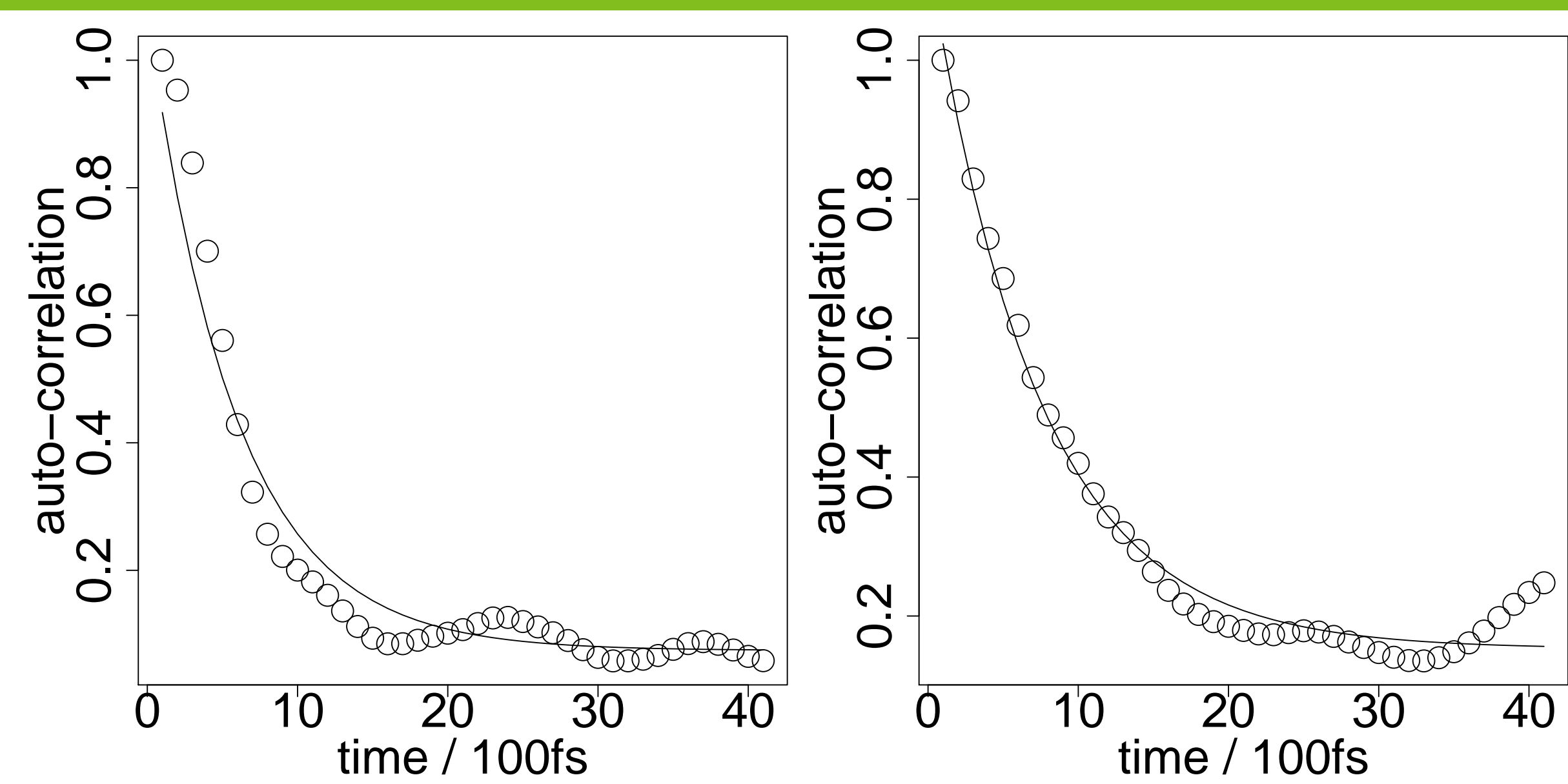
Forces occurring in molecular dynamics fluctuate over time, yielding characteristic force distributions. While the  $\sigma_i^{SASA}$  term models the mean force between solute and solvent, the variance of the force distributions are coupled to the friction parameter  $\gamma_i$ :

$$\langle (\mathbf{f}_i^{stoch})^2 \rangle \tau^{solv} = 6 m_i \gamma_i k_B T. \quad (5)$$

Here,  $\langle (\mathbf{f}_i^{stoch})^2 \rangle$  is the mean correlation of the friction force and  $\tau^{solv}$  is the autocorrelation time of the solvent friction. Using the fractional solvent accessibility  $\omega_i$  as scaling factor, we can derive the atom-specific friction parameter  $\gamma_i^0$ :

$$\gamma_i^0 = \frac{\tau^{solv}}{6 k_B T} \cdot \frac{\langle (\mathbf{f}_i^{stoch}(t) - \langle \mathbf{f}_i^{stoch} \rangle)^2 \rangle}{m_i} \cdot \frac{1}{\omega_i(t)}. \quad (6)$$

## Autocorrelation



(a) d1luqa\_Gly1 CA (b) d1luqa\_Asn34 ND2

Fig. 3 : Exemplary exponential fits (solid line) of the auto-correlation function (circles) of the solvation forces on atoms C, N, O and S. The unit lag of the auto-correlation functions corresponds to 100 fs of simulated time.

## $\gamma_i^0$ Parameters

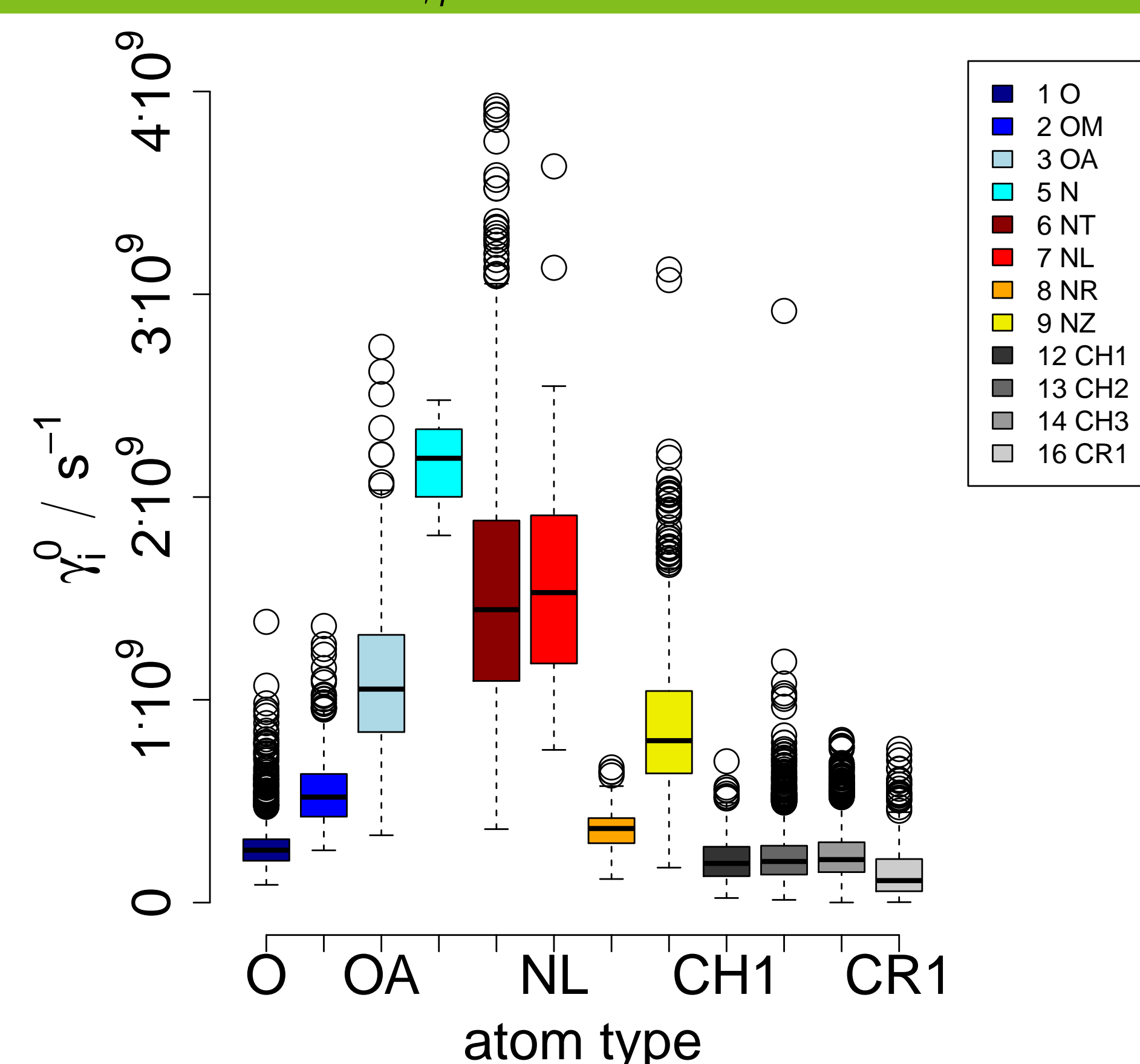


Fig. 4 : Boxplot of distributions of  $\gamma_i^0$  parameters.

## References

- [1] J. R. Allison, K. Boguslawski, F. Fraternali, and W. F. van Gunsteren. A refined, efficient mean solvation force model that includes the interior volume contribution. *J Phys Chem B*, 115:4547–4557, 2011.
- [2] F. Fraternali and W. F. van Gunsteren. An efficient mean solvation force model for use in molecular dynamics simulations of proteins in aqueous solution. *J Mol Biol*, 256(5):939–948, 1996.
- [3] W. Hasel, T. Hendrickson, and W. C. Still. A rapid approximation to the solvent accessible surface areas of atoms. *Tetrahedron Computer Methodology*, 1(2):103–116, 1988.
- [4] J. Kleinjung and F. Fraternali. Design and application of implicit solvent models in biomolecular simulations. *Current Opinion in Structural Biology*, 25:126–134, 2014.
- [5] J. Kleinjung, W. R. P. Scott, J. R. Allison, W. F. van Gunsteren, and F. Fraternali. Implicit solvation parameters derived from explicit water forces in large-scale molecular dynamics simulations. *J Chem Theor Comp*, 8:2391–2403, 2012.