

Testing the NCI integrals: the A β 42 dimer

Francesca Peccati

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Introduction

The NCI methodology

The NCI method identifies non-covalent interactions in the three-dimensional space by constructing a cubic grid around the system and calculating: i) the electron density (ρ) and ii) the reduced density gradient s at each point of the grid.

$$s(\mathbf{r}) = \frac{1}{C_s} \frac{|\vec{\nabla}\rho(\mathbf{r})|}{\rho(\mathbf{r})^{4/3}}$$

The low ρ and low s regions of space correspond to non-covalent interactions. The sign of the second density Hessian eigenvalue λ_2 is used to differentiate between attractive (negative $sign(\lambda_2)$) and repulsive (positive $sign(\lambda_2)$) interactions.

NCI integrals

We can integrate the density ρ in the regions of space corresponding to non-covalent interactions (using a cutoff of s) according to different ranges of $\text{sign}(\lambda_2)\rho$. The simplest partition is the following:

- a term corresponding to strong attractive interactions (high ρ , negative $\text{sign}(\lambda_2)$);
- a term corresponding to strong repulsive interactions (high ρ , positive $\text{sign}(\lambda_2)$);
- a term corresponding to van der Waals interactions (low ρ)

Corresponding to three terms, attractive, repulsive and van der Waals, that can be calculated for each geometry

Which density? Which NCI mode?

To compute ρ and s of large systems, we use a *promolecular density*, a molecular density obtained as sum of predetermined atomic densities.

There are essentially three types of NCI calculation:

- Intramolecular: all non-covalent interactions within the given system are computed;
- Intermolecular: only non-covalent interactions between two fragments are computed;
- ligand: only non-covalent interaction in a given range around a fragment are computed.

By defining the relevant fragments in combination with these three binding modes, we have an extreme flexibility in choosing which non-covalent interactions to study.

Aim

Aim

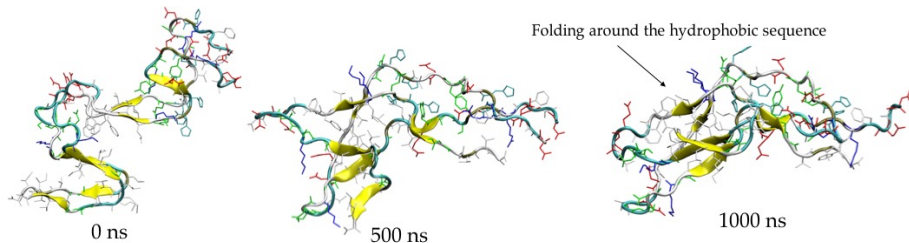
We want to follow the evolution of the three terms (attractive, repulsive and van der Waals) along a dynamics trajectory to correlate integral values with conformational changes.

We want to verify if these integrals allow us to follow (and quantify) non-covalent interaction changes associated with structural modifications.

A Bezier function is used to smooth the plots representing the integrals as a function of time.

1 μ s dynamics on a dimer extracted from PDB 2NAO

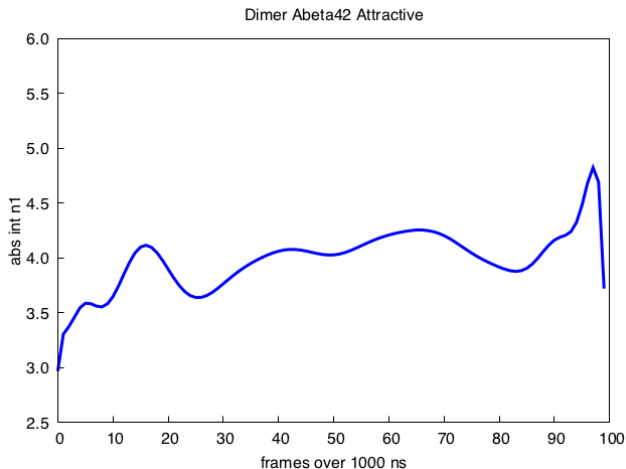
The test system is a dimer of the A β 42 extracted from the fibril structure of PDB 2NAO. The initial geometry of the dimer is that of the fibril; a 1 μ s dynamics in explicit solvent (water) simulation is run to observe the folding.

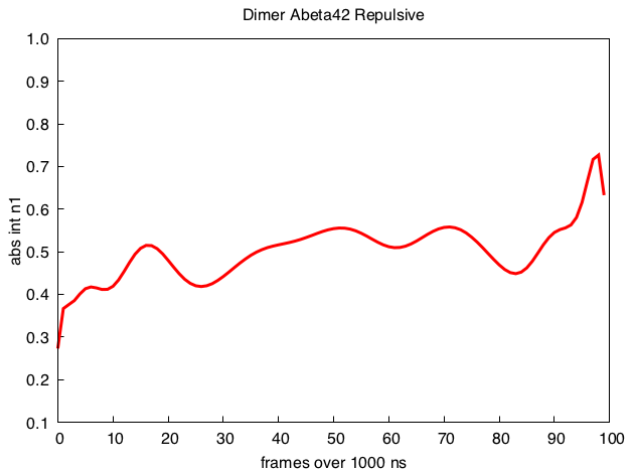


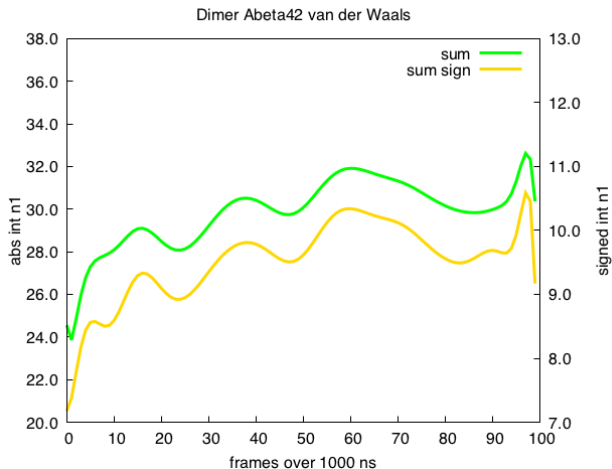
Yellow: β -sheet secondary structure.

Details

Integration ranges of $\text{sign}(\lambda_2)\rho$ -0.1 to -0.02 (attractive), -0.02 to 0.02 (van der Waals) and 0.02 to 0.2 (repulsive) - all residues. An *intermolecular* calculation is performed: we are looking at the total interaction between the two A β 42 monomers.

Integral attractive $\text{sign}(\lambda_2)\rho$ -0.1 to -0.02

Integral repulsive $\text{sign}(\lambda_2)\rho$ 0.02 to 0.1

Integral van der Waals $\text{sign}(\lambda_2)\rho$ -0.02 to 0.02

Comments

We plot two different functions for the van der Waals term according to the sign of λ_2 : since the van der Waals range encompasses negative and positive values of $\text{sign}(\lambda_2)\rho$, we show the trend of both $\sum \rho$ (sum) and $\sum \text{sign}(\lambda_2)\rho$ (sum sign).

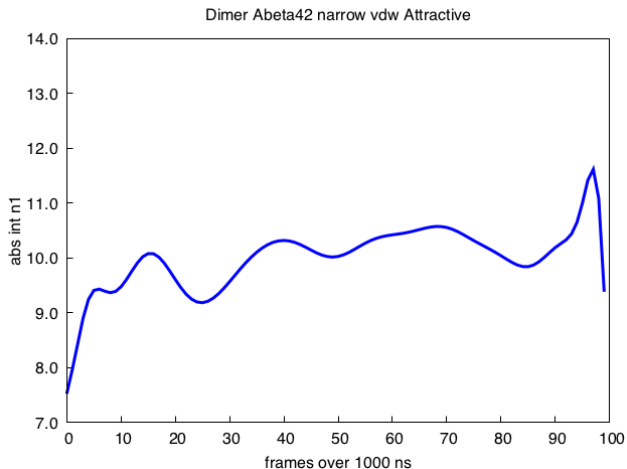
The evolution of the three terms over the 1 μs simulation has similar shape. This means that the potential energy is distributed evenly among the attractive, repulsive and van der Waals terms. The attractive and repulsive terms are more similar to each other than the van der Waals one. With this partition, van der Waals is dominating in terms of intensity. An increase of the three integrals over time is observed. *Natura non facit saltus*: starting from an equilibrium geometry, changes in the attractive term are compensated by a corresponding change in the repulsive term (and *viceversa*).

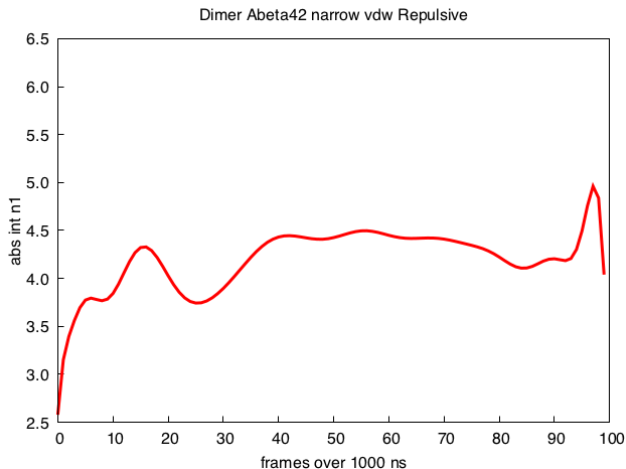
The values of the integrals follow the order van der Waals \gg attractive $>$ repulsive. This indicates that most of the non-covalent interactions in this system fall into the van der Waals range. What happens if we change the partitioning of the system and use a narrower range for van der Waals interactions?

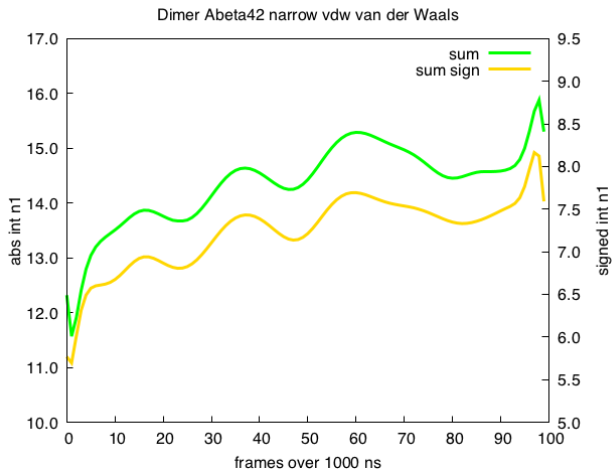
Intermolecular NCI - narrow van der Waals range

Details

Integration ranges of $\text{sign}(\lambda_2)\rho$ -0.1 to -0.01 (attractive), -0.01 to 0.01 (van der Waals) and 0.01 to 0.1 (repulsive) - all residues. We want to study how a different definition of the ranges corresponding to the three terms affects the evolution of the integrals.

Integral attractive $\text{sign}(\lambda_2)\rho$ -0.1 to -0.01

Integral repulsive sign(λ_2) ρ 0.01 to 0.1

Integral van der Waals $\text{sign}(\lambda_2)\rho$ -0.01 to 0.01

Comments

The evolution of the attractive, repulsive and van der Waals terms in this partitioning is similar to the results obtained with the previous one. This is encouraging, because it suggests that we can use the same integration ranges across different systems and expect robust results.

Interestingly, after 400 ns (frame 40) the attractive and repulsive terms are fairly constant, while the van der Waals term keeps growing. Now the relative size of the integrals is as follows: van der Waals \sim attractive $>$ repulsive.

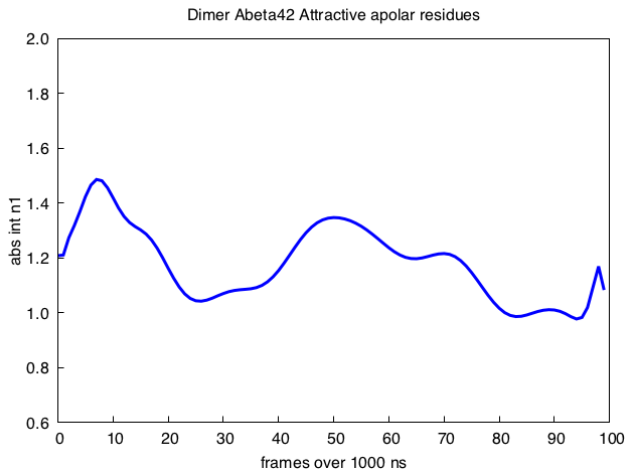
While the shape of the integrals as a function of time remains fairly constant, the relative intensities of the three terms changes, as points that were previously assigned to the van der Waals range are now assigned to attractive and repulsive interactions.

Intermolecular NCI - apolar residues - standard range

Details

Integration ranges of $\text{sign}(\lambda_2)\rho$ -0.1 to -0.02 (attractive), -0.02 to 0.02 (van der Waals) and 0.02 to 0.1 (repulsive) - residues 17 to 20 and 30 to 42 (hydrophobic). Again, we compute NCIs in the intermolecular mode, i.e. looking only at the interaction between the two dimers.

Integral attractive $\text{sign}(\lambda_2)\rho$ -0.1 to -0.02 residues 17 to 20 and 30 to 42



Integral repulsive sign(λ_2) ρ 0.02 to 0.1 residues 17 to 20 and 30 to 42



Integral van der Waals $\text{sign}(\lambda_2)\rho$ -0.02 to 0.02 residues 17 to 20 and 30 to 42

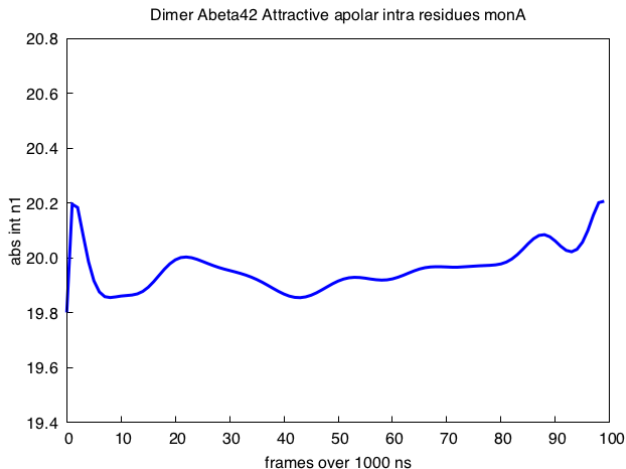


Comments

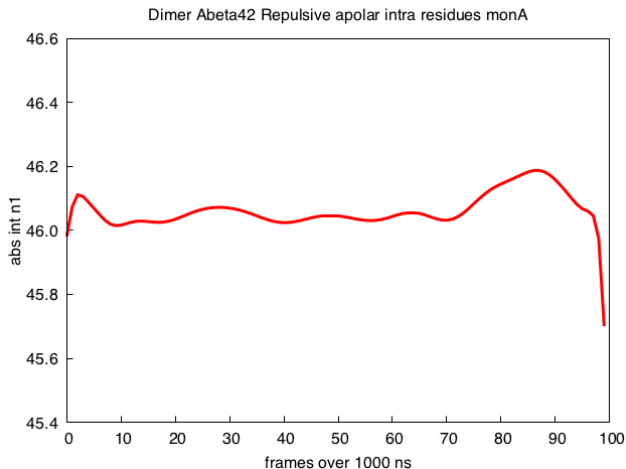
The *intermolecular* van der Waals contact between hydrophobic residues is reduced along the trajectory. This seems to suggest that indeed the structure of the fibrils does maximize the *intermolecular* packing of hydrophobic residues *between* the two monomers. However, just by looking at the trajectory, however, it seems that the system evolves too maximize hydrophobic contacts between the β sheet regions. How can we explain then that the *intermolecular* van der Waals term decreases? We expect it to be compensated by an increase of the *intramolecular* van der Waals term of the two monomers.

Intramolecular NCI - apolar residues - Monomer A

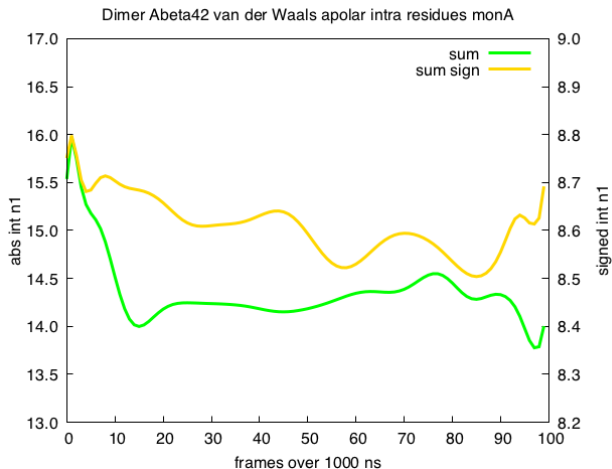
Integral attractive monomer A residues 17 to 20 and 30 to 42



Integral repulsive monomer A residues 17 to 20 and 30 to 42

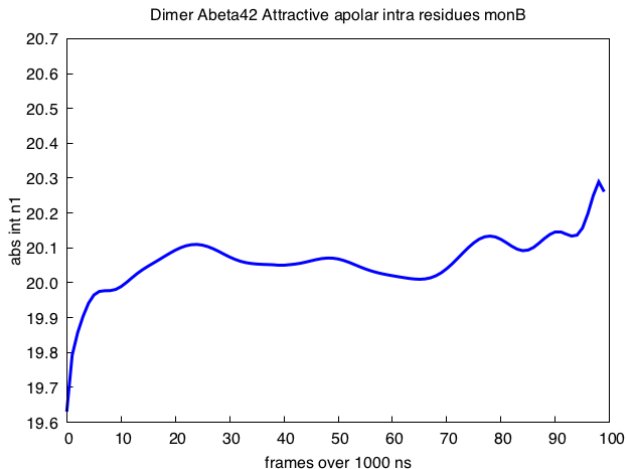


Integral van der Waals monomer A residues 17 to 20 and 30 to 42



Intramolecular NCI - apolar residues - Monomer B

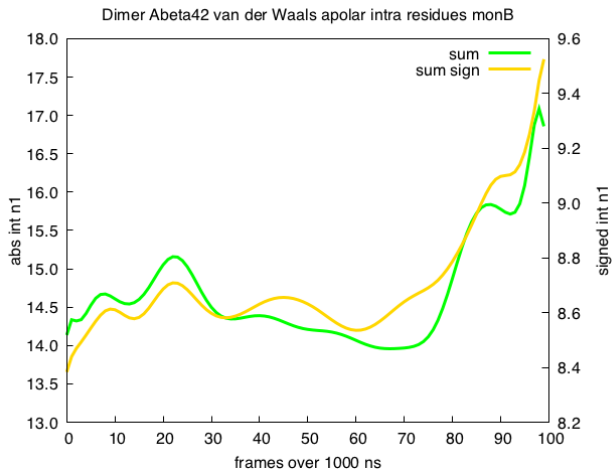
Integral attractive monomer B residues 17 to 20 and 30 to 42



Integral repulsive monomer B residues 17 to 20 and 30 to 42



Integral van der Waals monomer B residues 17 to 20 and 30 to 42



Comments

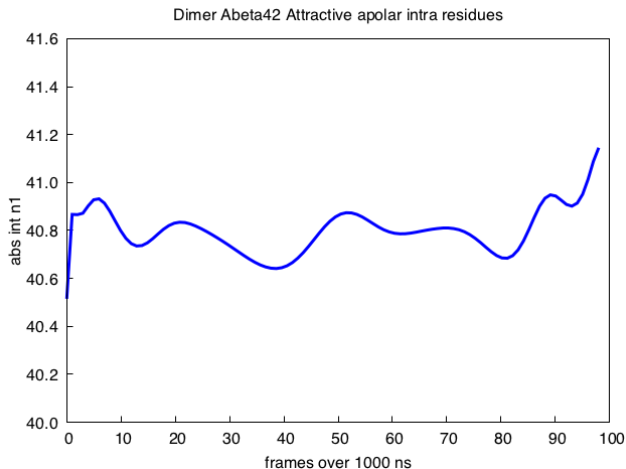
While in monomer A vdW contacts seem to be slightly decreasing, in monomer B we observe a sharp increase of the vdW term, which compensates for the loss of intermolecular interactions.

To summarize, we have seen that the dynamics trajectory evolves from the fibril structure (initial geometry) to a new dimer architecture where a partial loss of intermolecular hydrophobic contacts is compensated by a sharp increase of intramolecular hydrophobic contacts in monomer B.

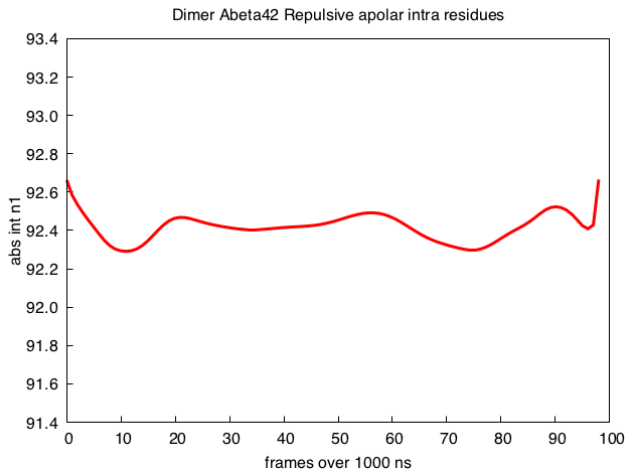
Finally, to see how these two phenomena (loss of intermolecular and gain of intramolecular hydrophobic contacts) balance out, we can look at these two interactions as a whole, with a new *intramolecular* NCI calculation considering the hydrophobic residues of the two monomers at the same time.

Intramolecular NCI - apolar residues - standard range

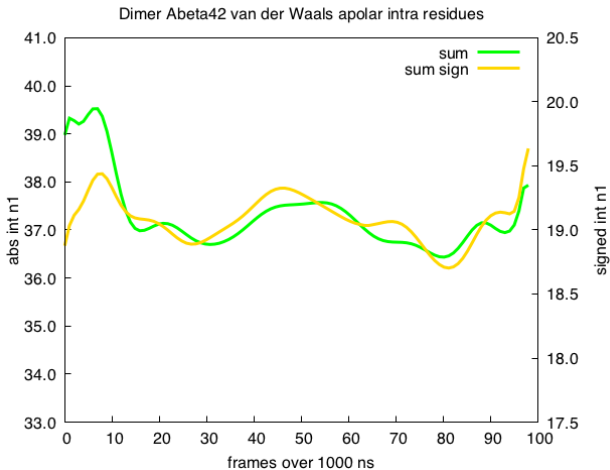
Integral attractive $\text{sign}(\lambda_2)\rho$ -0.1 to -0.02 residues 17 to 20 and 30 to 42



Integral repulsive sign(λ_2) ρ 0.02 to 0.1 residues 17 to 20 and 30 to 42



Integral van der Waals $\text{sign}(\lambda_2)\rho$ -0.02 to 0.02 residues 17 to 20 and 30 to 42



Comments

After the initial 400 ns (40 frames) corresponding to equilibration, the intramolecular van der Waals term remains fairly constant along the trajectory, meaning that globally hydrophobic residues maintain the same contacts.

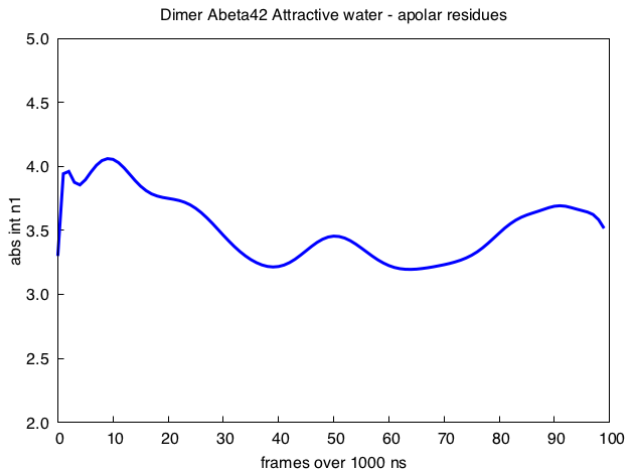
So, to summarize:

- NCI transitions are smooth, with sharp changes in the attractive (repulsive) term being compensated by opposite sign repulsive (attractive) fluctuations;
- globally, after the initial 400 ns of equilibration (40 frames), van der Waals interactions of hydrophobic residues 17 to 20 and 30 to 42 remain constant, but as the result of a compensation between loss of intermolecular and gain of intramolecular contacts;
- by combining the definition of NCI fragments and calculation mode, we can decompose NCI interactions at will.

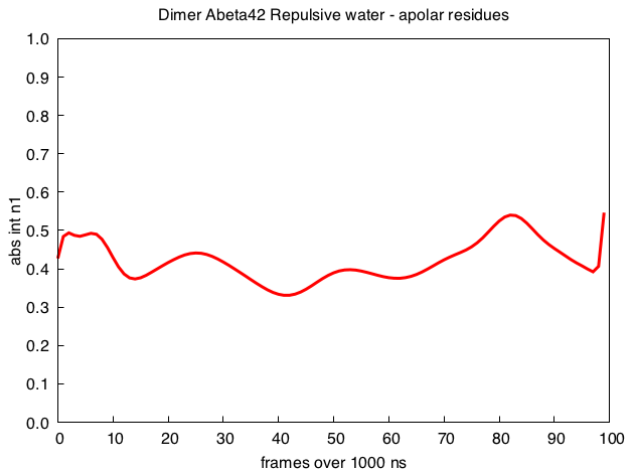
As an independent confirmation of the observation that van der Waals interactions of hydrophobic residues 17 to 20 and 30 to 42 remain constant in the second part of the trajectory, we can look at solvation: we can perform an *intermolecular* NCI calculation between hydrophobic residues and the explicit water molecules used as solvent.

Solvation

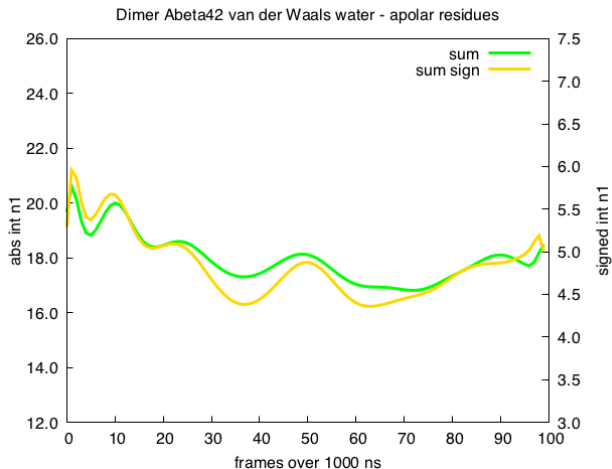
Intermolecular residues 17 to 20 and 30 to 42 - water - attractive



Intermolecular residues 17 to 20 and 30 to 42 - water - repulsive



Intermolecular residues 17 to 20 and 30 to 42 - water - van der Waals



Comments

The smooth evolution of the three solvation integrals with the hydrophobic residues suggests that no drastic change in solvation is observed along the trajectory.