Coarse grained calculation of molecular polarizability of proteins

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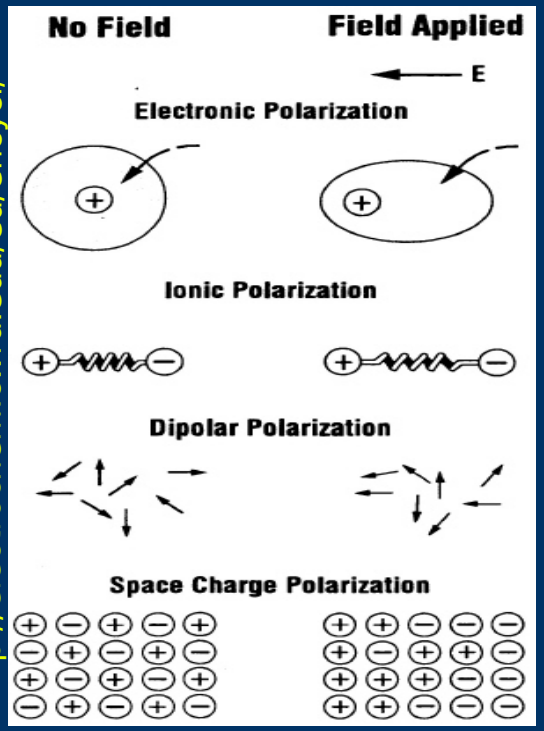
Background

- Change of refractive index of antibody antigen solution upon antigen binding
  - related to dielectric constant
  - related to polarization of solution
- Change of polarization due to antigen binding
  - calculation of molecular polarizability
    - response to external electric field
      - electronic, atomic, orientation
- Not included in current molecular mechanics force fields

Relation of refractive index to dieletcric constant and polarization

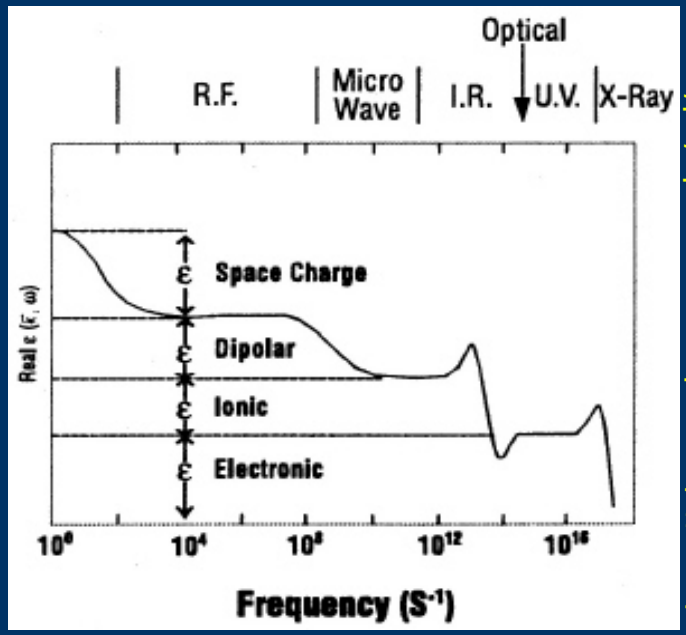


http://electrochem.cwru.edu/ed/encycl/

$$n = \sqrt{\varepsilon}$$

$$\varepsilon = 1 + 4 * pi * \chi$$

$$\chi = \alpha / V$$



http://electrochem.cwru.edu/ed/encycl/

Dielectrics

- Refractive index

$$n = \frac{c}{v_{\mathrm{ph}}}$$

$$n = \sqrt{\epsilon_r \mu_r}$$

relative permittivity
relative permeability ~1

Dielectric constant

Polarizability

$$\frac{\varepsilon_r - 1}{\varepsilon_r + 2} = \frac{\rho N_A \alpha}{3 M \varepsilon_0}$$

$$\frac{\varepsilon - 1}{\varepsilon + 2} = \frac{N \bullet \alpha}{3 \bullet \varepsilon_0}$$

From electronic polarization to molecular polarizability

Induced dipole moment

Polarizability

External field + field due to induced dipoles

$$\mu_p = \alpha_p \left[F_p - \sum_{q \neq p}^{N} T_{pq} \mu_q \right]$$

Dipole field tensor

$$T_{pq} = \frac{\mathbf{1}}{r_{pq}^{3}} - \frac{\mathbf{3}}{r_{pq}^{5}} r$$

$$RM = F$$

Relay matrix

$$M = AF \text{ , where } A \equiv R^{-1} = \left[\alpha^{-1} + T \right]^{-1}$$

$$\alpha = \sum_{i,\, j=1}^{N} (A_{ij})$$

Molecular polarizability

- Point dipole model: history
  - Applequist: Basic model
  - Thole: Modified to avoid polarization catastrophe
  - Swart: Parametization for amino acids

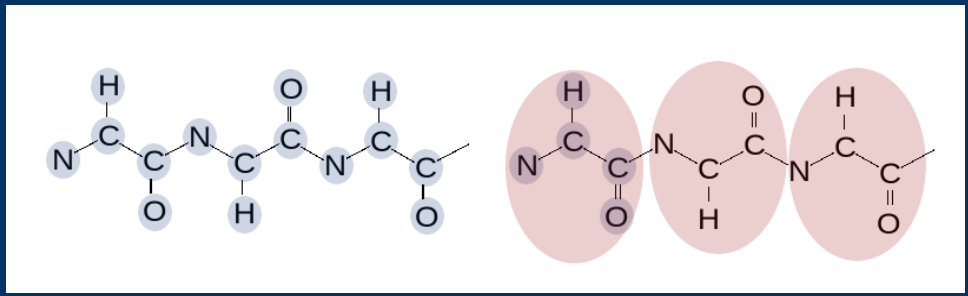
Applequist JACS (1972) 94:9

Thole B.T. Chemical Physics (1981) 59

Swart M et al. Journal of Computational Methods in Sciences and Engineering (2004) 4

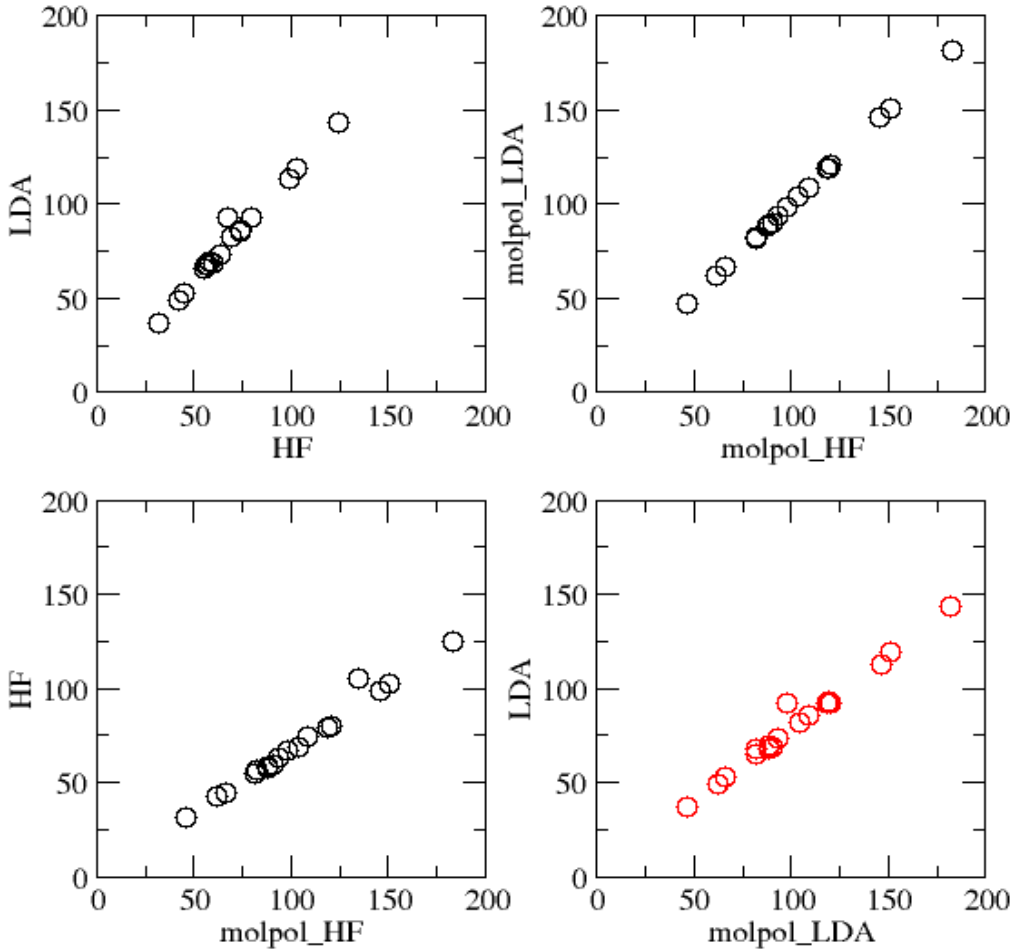
- **Coarse Graining (unit properties form atomic ones)**

- Molecule is divided into units
- Unit polarizability from atomic polarizabilities
- Unit tensor placed in the “center of polarizability” of each unit



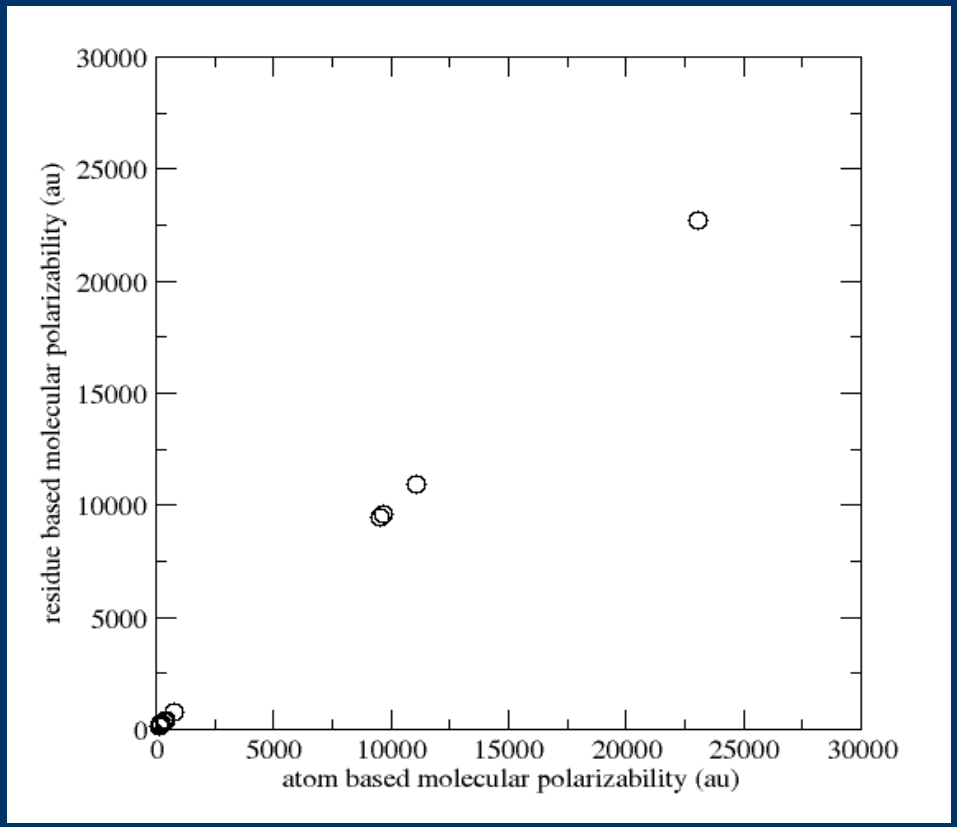
- Protein residues as unit

Molecular polarizability using point dipole model – validation of implementation



- Test case
  - Amino acid polarizabilities
  - Quantum mechanics vs. point dipole approximation
  - Good correlation but not exact values

Molecular polarizabilities using coarse graining



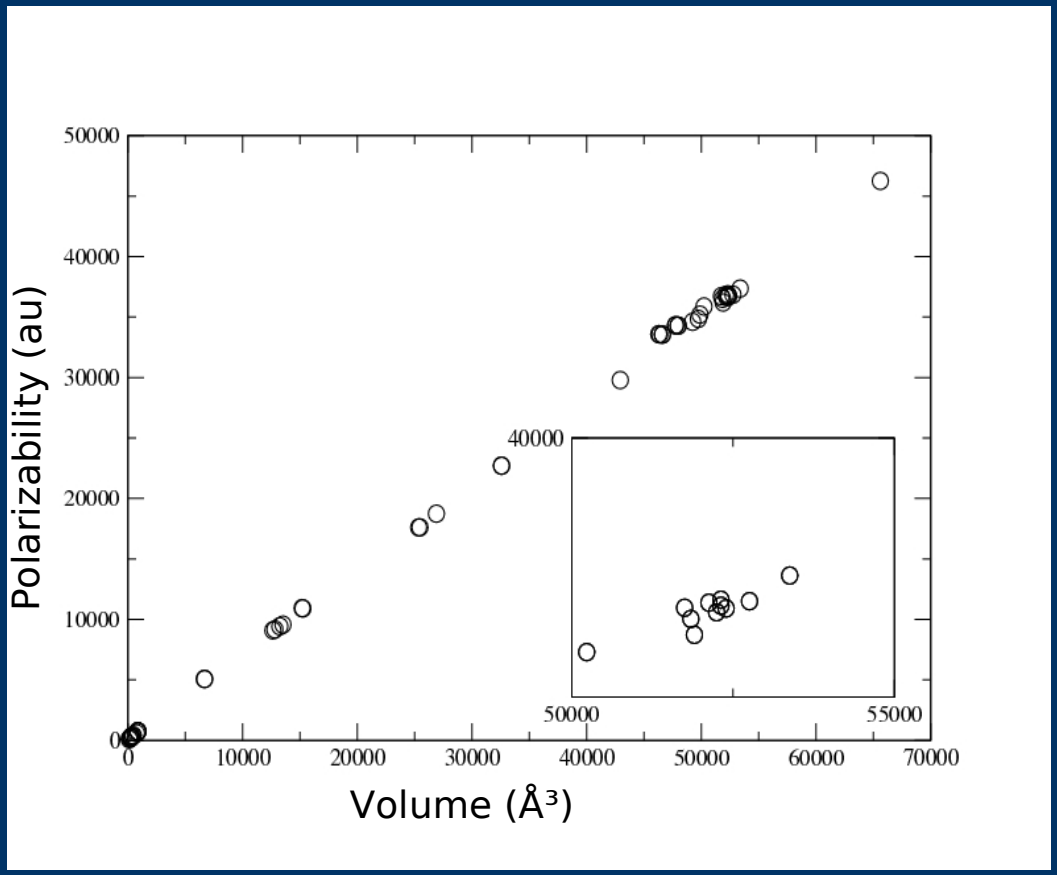
- Atom based and residue based average molecular polarizabilities of a set of 10 proteins and protein complexes

Test set

- 19 protein and ligand and antibody antigen complexes
- coordinates from PDB

Complex (PDB)	size (atoms)	Protein/AB	size (atoms)	Ligand/antigen	size (atoms)
1lkk	1153	P56-LCKSH2	1103	YEEI	50
1lkl	1140	P56-LCKSH2	1094	YEEG	46
1vac	4020	H-2KB	373	SIINFEKL	89
2ptc	2692	B-trypsin	2088	BPTI	604
2tgp	2691	Trypsinogen	2087	BPTI	604
2vaa	4026	H-2KB	373	RGYVYQGL	95
2vab	4020	H-2KB	373	FAPGNYPAL	89
2AJV	4393	cocaine-ab	4371	cocaine	22
2AK1	4379	cocaine-ab	4371	benzioc acid	9
2AJZ	4384	cocaine	4371	3-HYDROXY-8-METHYL-8-AZA-BICYCLO[3.2.1]OCTANE-2-CARBOXYLIC ACID METHYL ESTER (ECG)	15
2AJS	4394	cocaine	4371	3,6,9,12,15,18-HEXAOXAICOSANE-1,20-DIOL (P33)	24
2CGR	4289	gas-ab	4255	GAS	32
1VFB	3578	D1.3	2252	Lysozyme	1321
1C08	5508	Hyhel5	4187	Lysozyme	1321
2MPA	4452	Meningitis-ab	4376	Meningitis	72
2VAB	4020	mhc-sv	3931	SendaiVirus	89

Residue based molecular polarizabilities



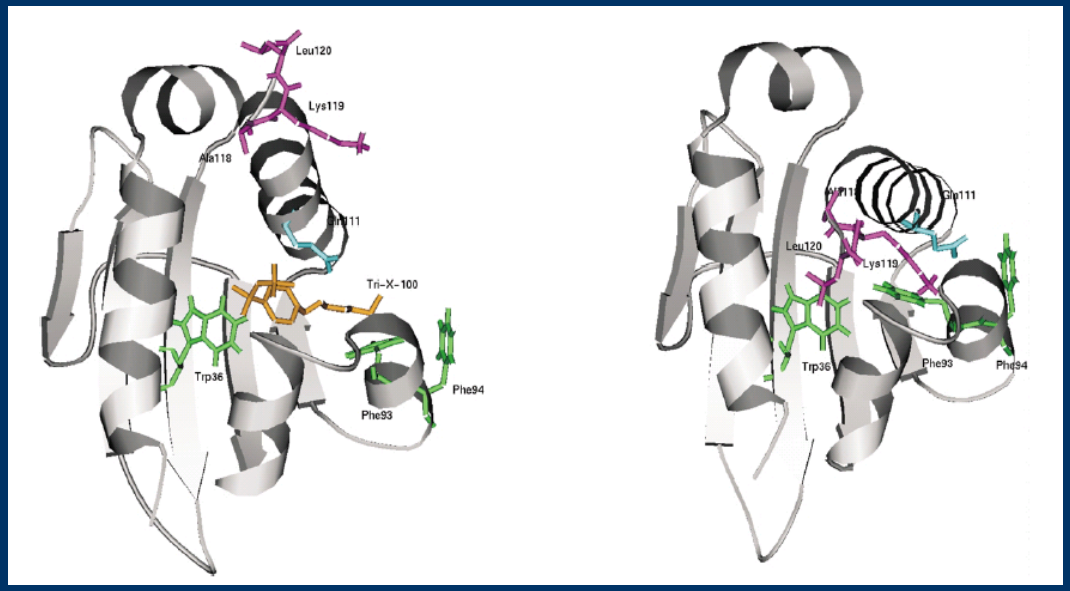
- Dependence of polarizability on size (volume) of the molecule
- Linear dependency breaks down at small scale
  - atom type and conformation dependent

Molecular polarizability – coarse graining and protein dynamics

- Dependency of molecular polarizability on conformation
- Residue based vs atomic calculation
- Correlation with structural changes
- Analysis of molecular polarizability from molecular dynamics simulations

Analysed proteins

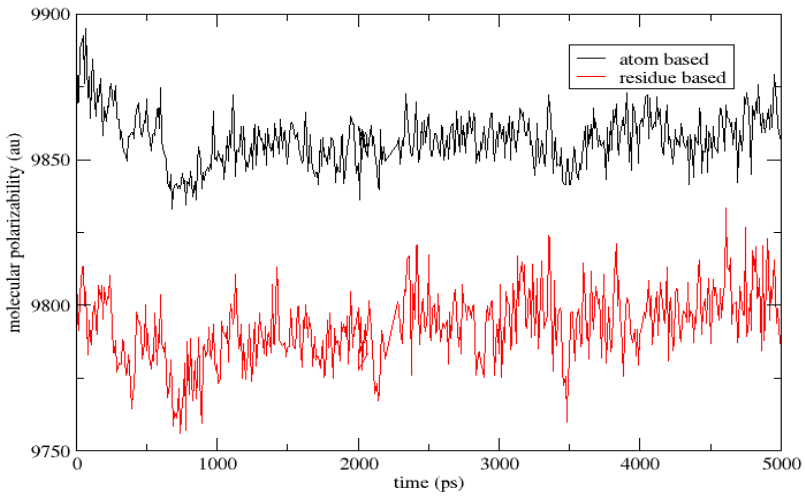
- Sterol carrier protein 2 like domain of human MFE-2 protein
- Phosphatic acid phosphatase

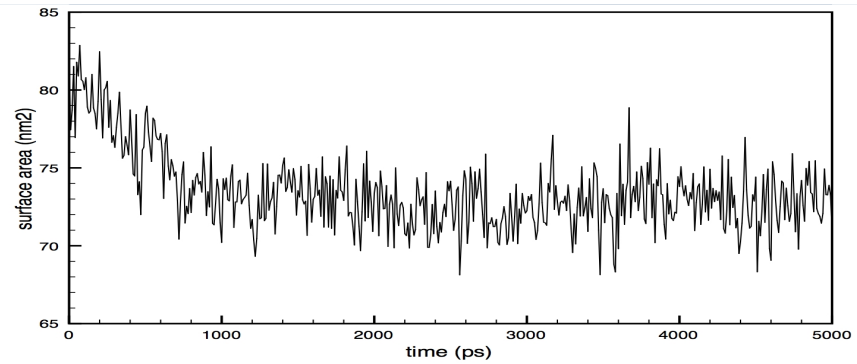


Lensink et al. J.Mol.Biol (2002) 323, 99-113

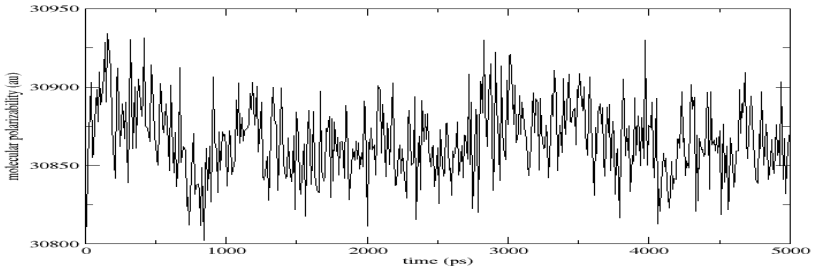
Sharma et al. Proteins (2005) 58, 295 - 308

Molecular polarizability from simulation of SCP2-like protein





- Molecular polarizability and surface area change in SCP2-l simulation
- Change of molecular polarizability correlates with initial conformational change in SCP2-l
- Dependency of atom positions



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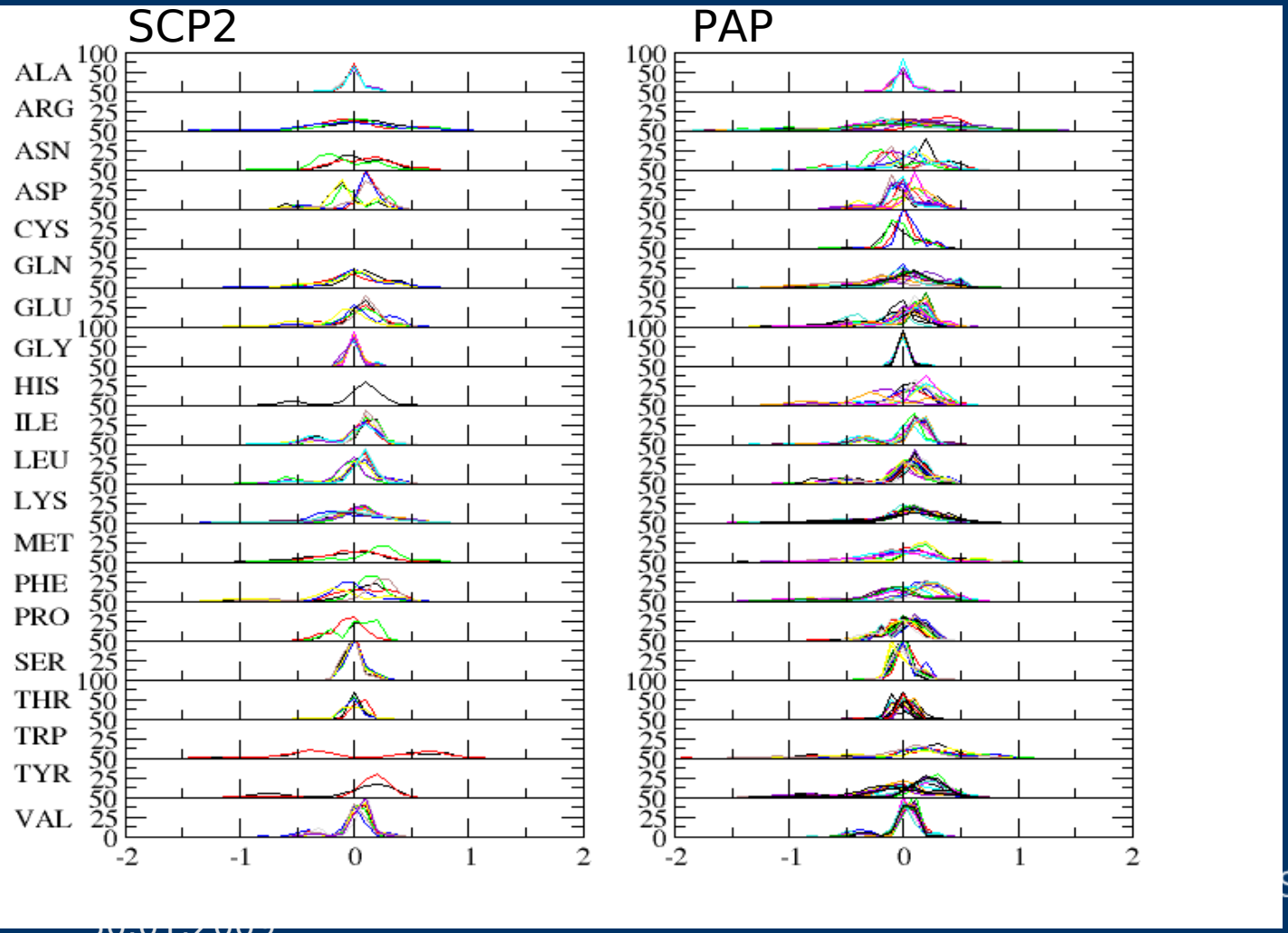
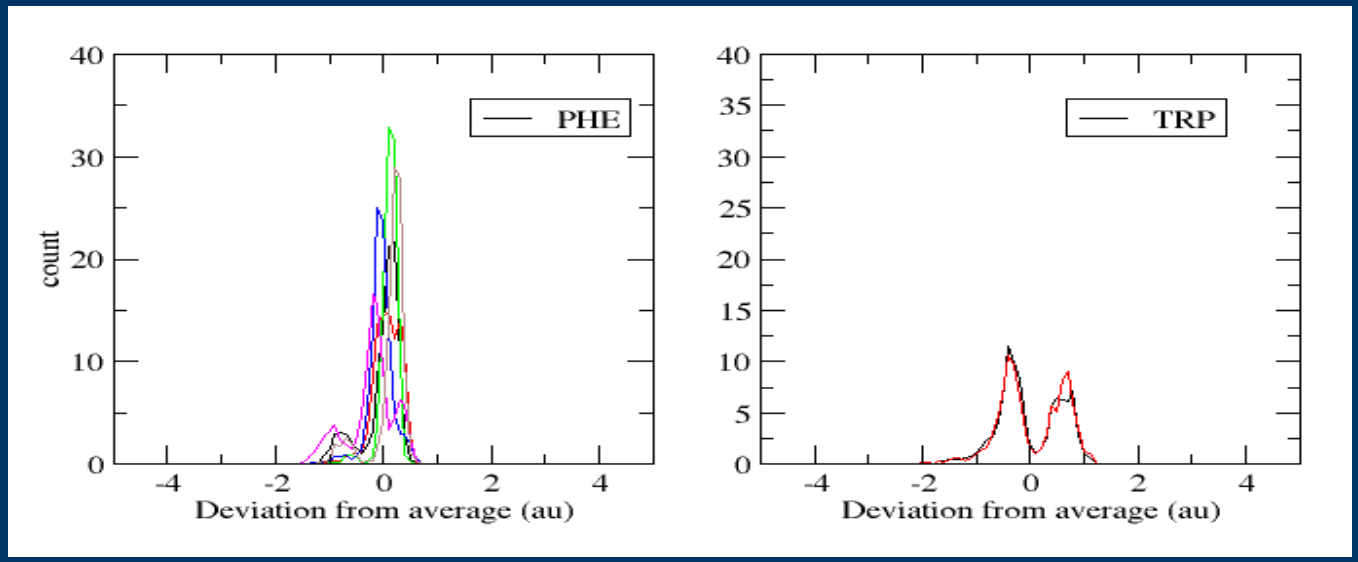
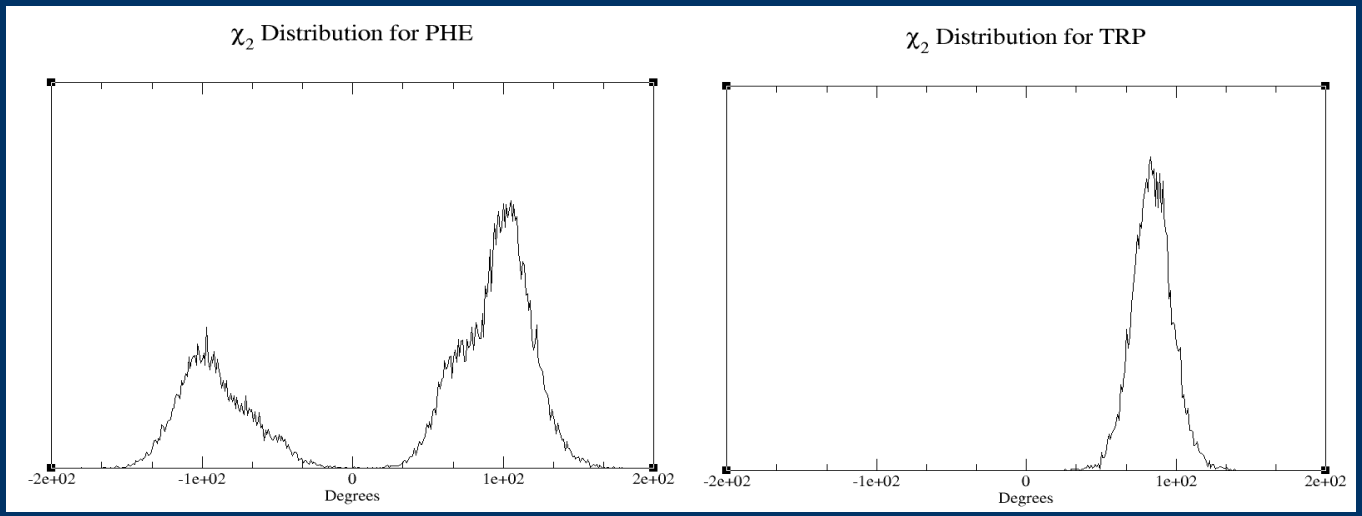
Comparison of atom based molecular polarizabilities of protein residues from simulation data



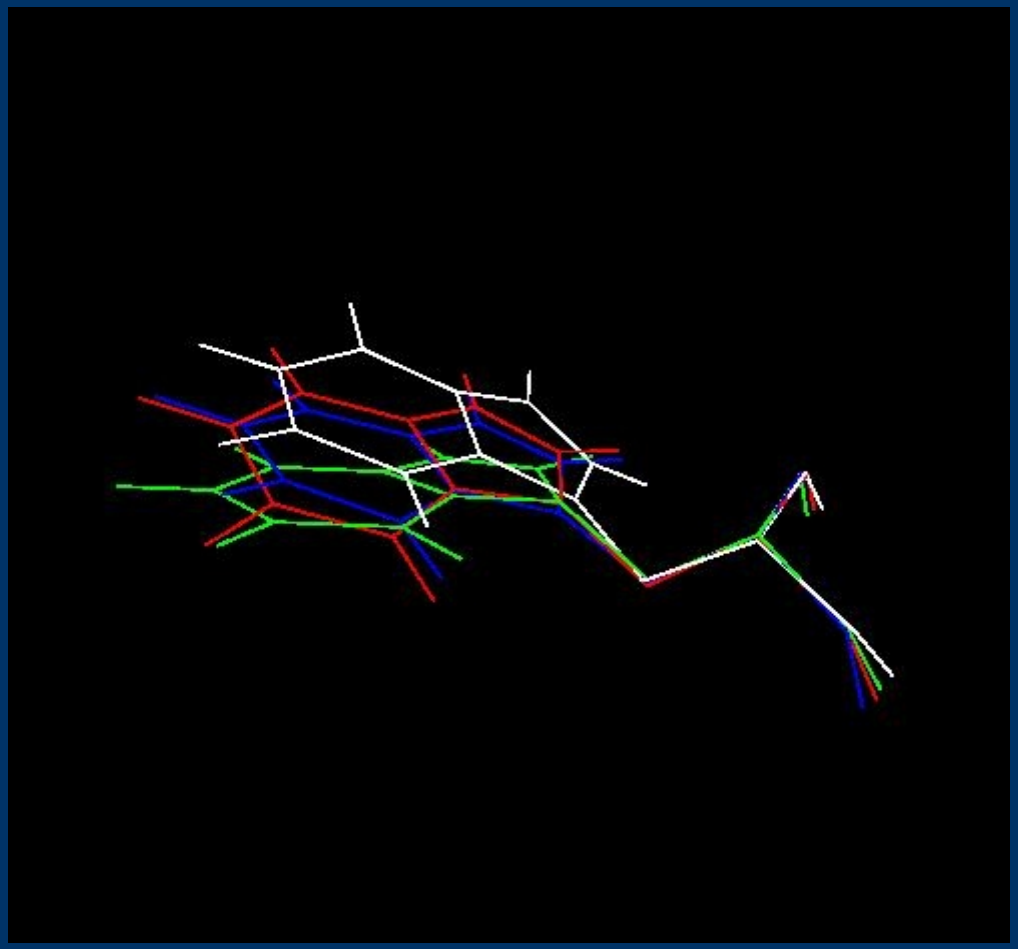
- Deviation of average polarizability of each sampled conformation from simulation average
- Same in different porteins
- Different dynamics due to location

Comparison of dihedral angle and molecular polarizability distributions



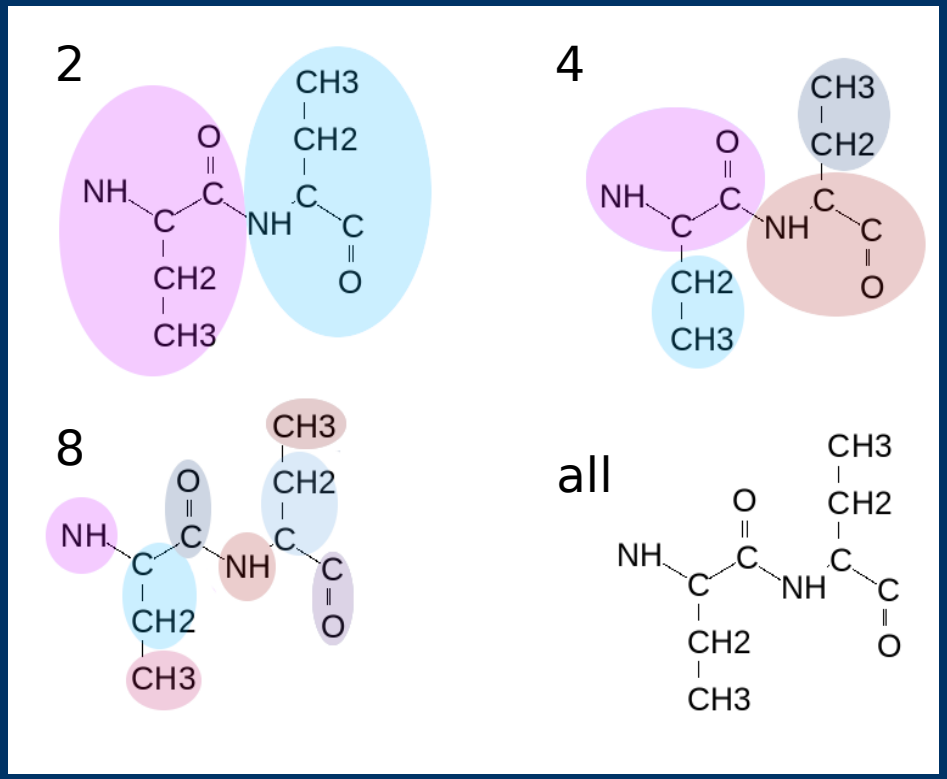


Tryptophan conformations having different polarizabilities



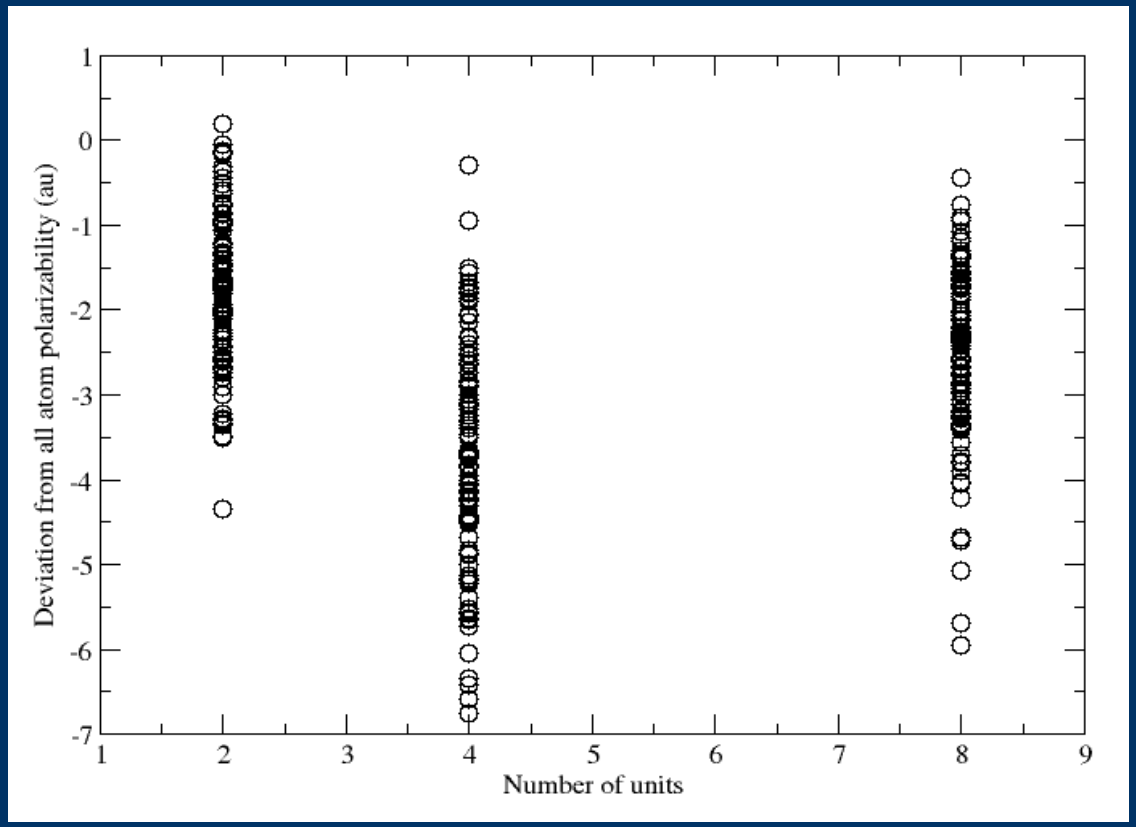
- Largest deviations of polarizabilities
  - red and green
- “Peak” polarizabilities
  - blue and white

Effect of unit definition on results of coarse grained calculation of molecular polarizability



- Dipeptides divided into 2, 4, and 8 units
- 2 units corresponds to residue based coarse graining
- All atom is same as one atom in each group

Effect of unit definition on results of residue based calculation of molecular polarizability



Deviation of unit based average molecular polarizability from atom based average molecular polarizability of different dipeptides

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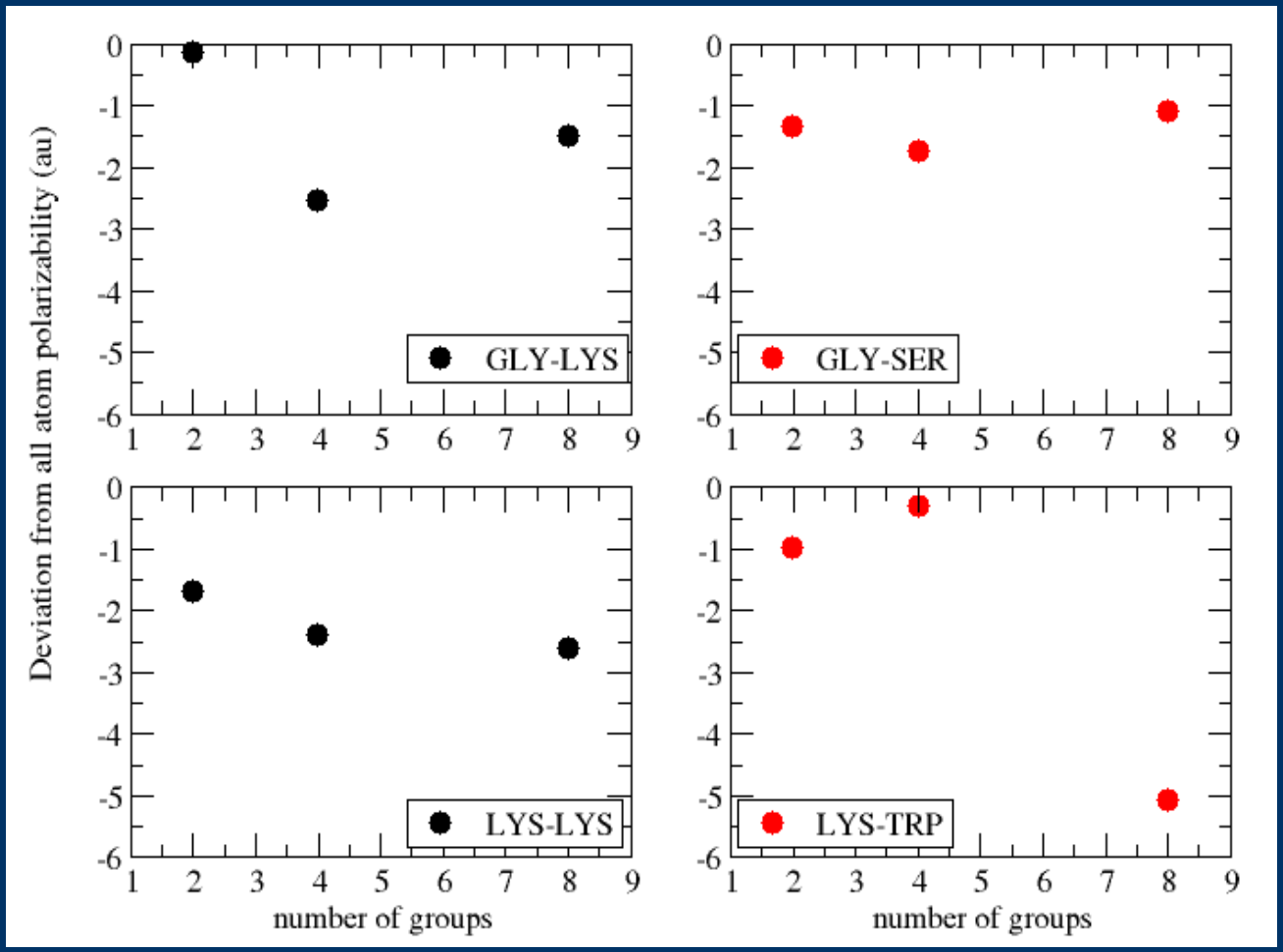
Examples of effect of unit definition



- Deviation of unit based polarizability from atom based polarizability for four different dipeptides
- Justification of using residue as polarization unit

Conclusions

- Linear relationship between the atomic and coarse-grained calculation of molecular polarizability
- Atomic and coarse-grained based calculations show same average behavior altough variation on coarse-grained values is bigger
- Molecular polarizability of protein residues varies slightly according to location in the protein structure (allowed dynamics)

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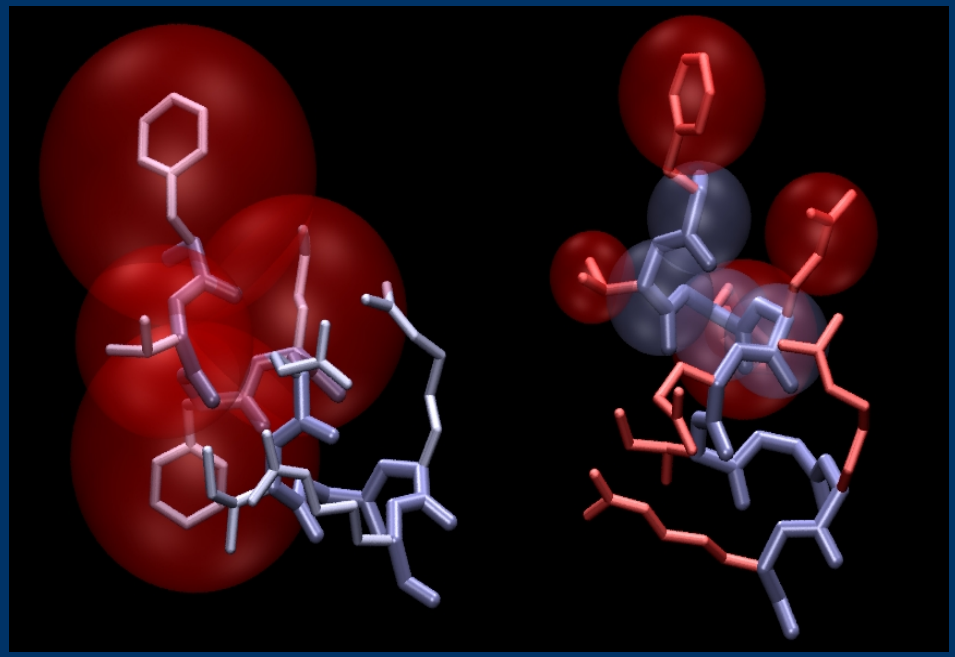

Thank you for your attention