International Spring School Statistical Thermodynamics, Santiago de Chile
Wednesday, November 29, 2017
Lecture 20

Accounting for polarisation effects in bio-molecular simulation

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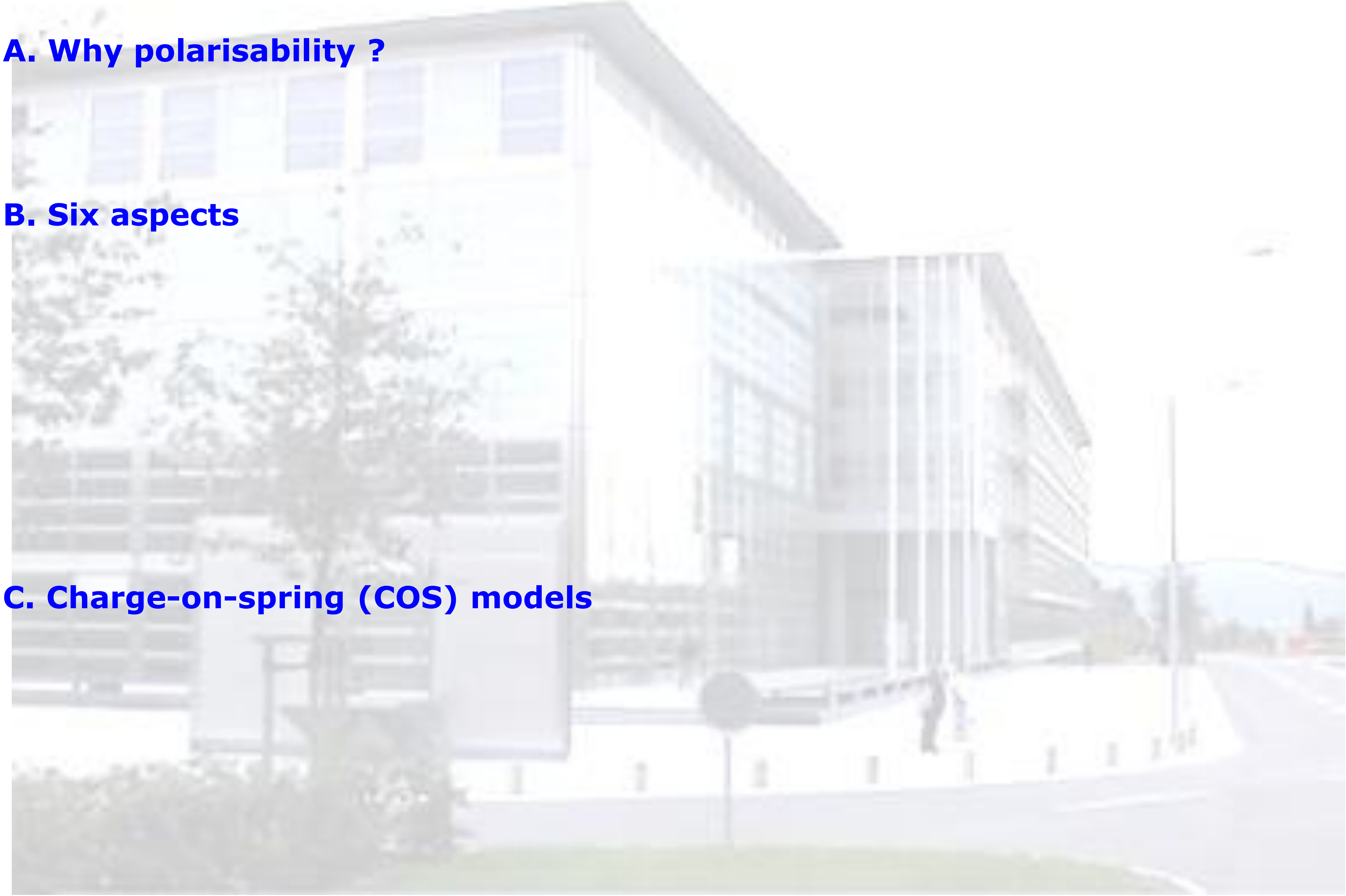
Inclusion of polarisability in molecular models



A. Why polarisability ?

B. Six aspects

C. Charge-on-spring (COS) models

Inclusion of polarisability in molecular models

A. Why polarisability ?

1. Effects of polarisability

B. Six aspects

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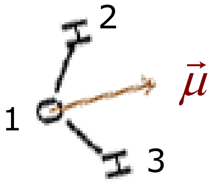
Effects of polarisability

I Liquids, water

1. Dipole moment of a water molecule:

$$\vec{\mu} = \sum_{i=1}^{3} q_i \vec{r}_i$$



gas phase = 1.85 Debye
liquid phase ~ 2.5 Debye

water molecule is polarised when immersed in water

2. Polarisation energy of liquid water

~ 10 kJ/mol

potential energy: 42 kJ/mol

polarisation energy ~ 25%

1 eV = 97 kJ/mol or 1 kJ/mol = 0.01 eV

1 kcal/mol = 4.184 kJ/mol or 1 kJ/mol = 0.24 kcal/mol

Effects of polarisability

3. **Macroscopic polarisation as function of the frequency ω of the oscillating electric field $\vec{E}$**

the dielectric permittivity $\varepsilon_r(\omega)$

is dependent on the frequency ω
of the oscillating field $\vec{E}(\omega)$

liquid water $\varepsilon_r(0) = \varepsilon_r(\text{static}) = 78$ electronic + orientation

$\varepsilon_r(\infty) = \varepsilon_r(\text{infinite freq.}) \approx 2-5$ only electronic

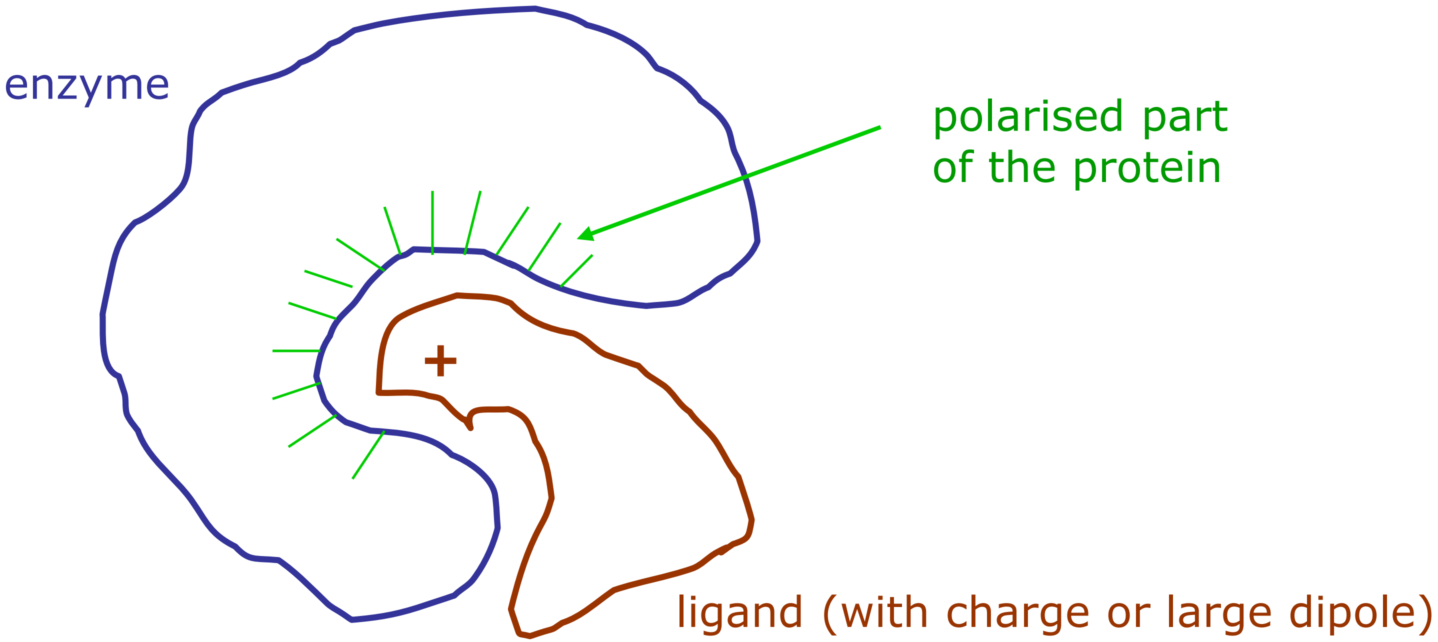
Consequence: gas phase water models
(e.g. derived using quantum-mechanical models)
will *not* represent liquid water,
if explicit polarisation is not included

Effects of polarisability

II Lipids and proteins in membranes

Carbon atoms of lipids can get polarised upon protein insertion

III Proteins, ligand binding



Protein can get polarised upon ligand binding

Inclusion of polarisability in molecular models

A. Why polarisability ?

1. Effects of polarisability

2. Limitations of non-polarisable force fields

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Limitations of non-polarisable force fields

1. Solvation of polar amino-acid side-chain analogs

One set of atomic charges and van der Waals parameters cannot reproduce both:

heat of vaporisation of the liquid } ***and*** { **free energy of solvation in polar solvent: water**

GROMOS **53A*5*** parameters | GROMOS **53A*6*** parameters

due to the different polarisability of these two environments.

Free energy of solvation in apolar solvent, cyclohexane, is compatible with both using a non-polarisable force field.

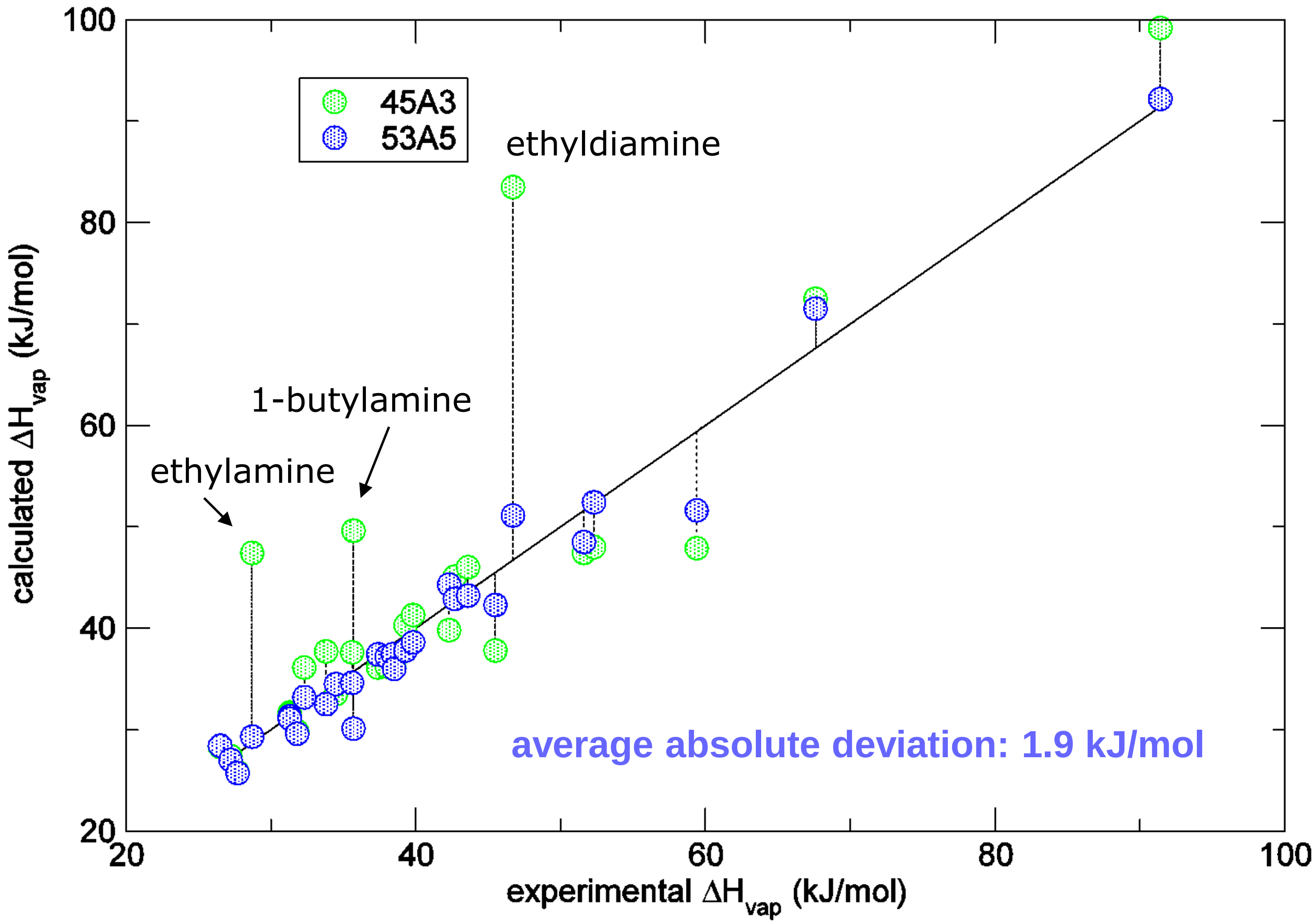
2. Solvation of dimethylether (DME)

Polarisable models yield better (free) energies (of solvation)

3. Hydrophobic solvation in water – ethylene glycol mixtures

Polarisable models can reproduce the maximum in the free enthalpy of solvation as function of ethylene glycol mole fraction

Heat of vaporization for pure liquids

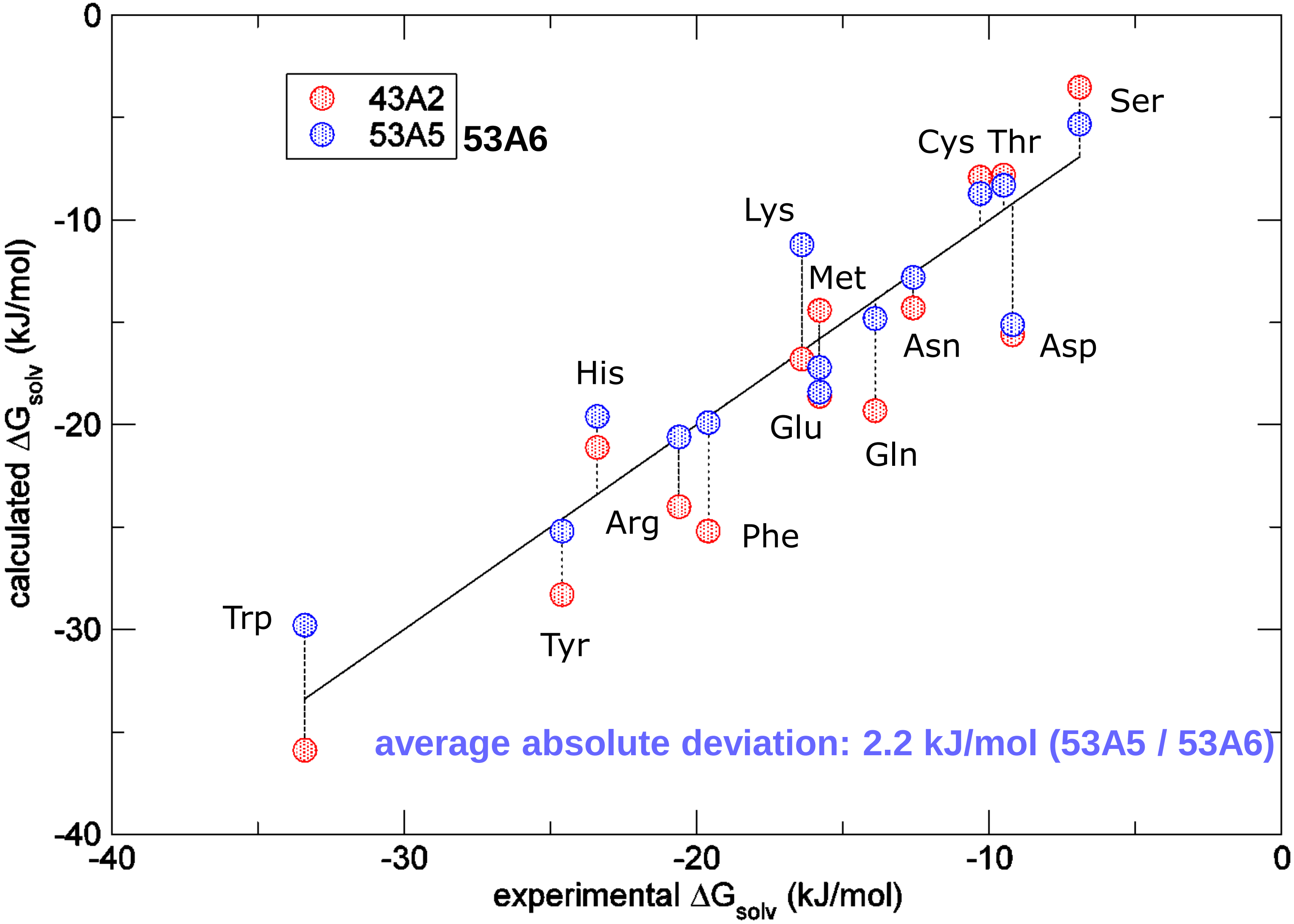


average absolute deviation: 1.9 kJ/mol

*Oostenbrink et al., J Comput. Chem. 25 (**2004**) 1656-1676*

Free energy of solvation in cyclohexane

amino acid analogues (polar)

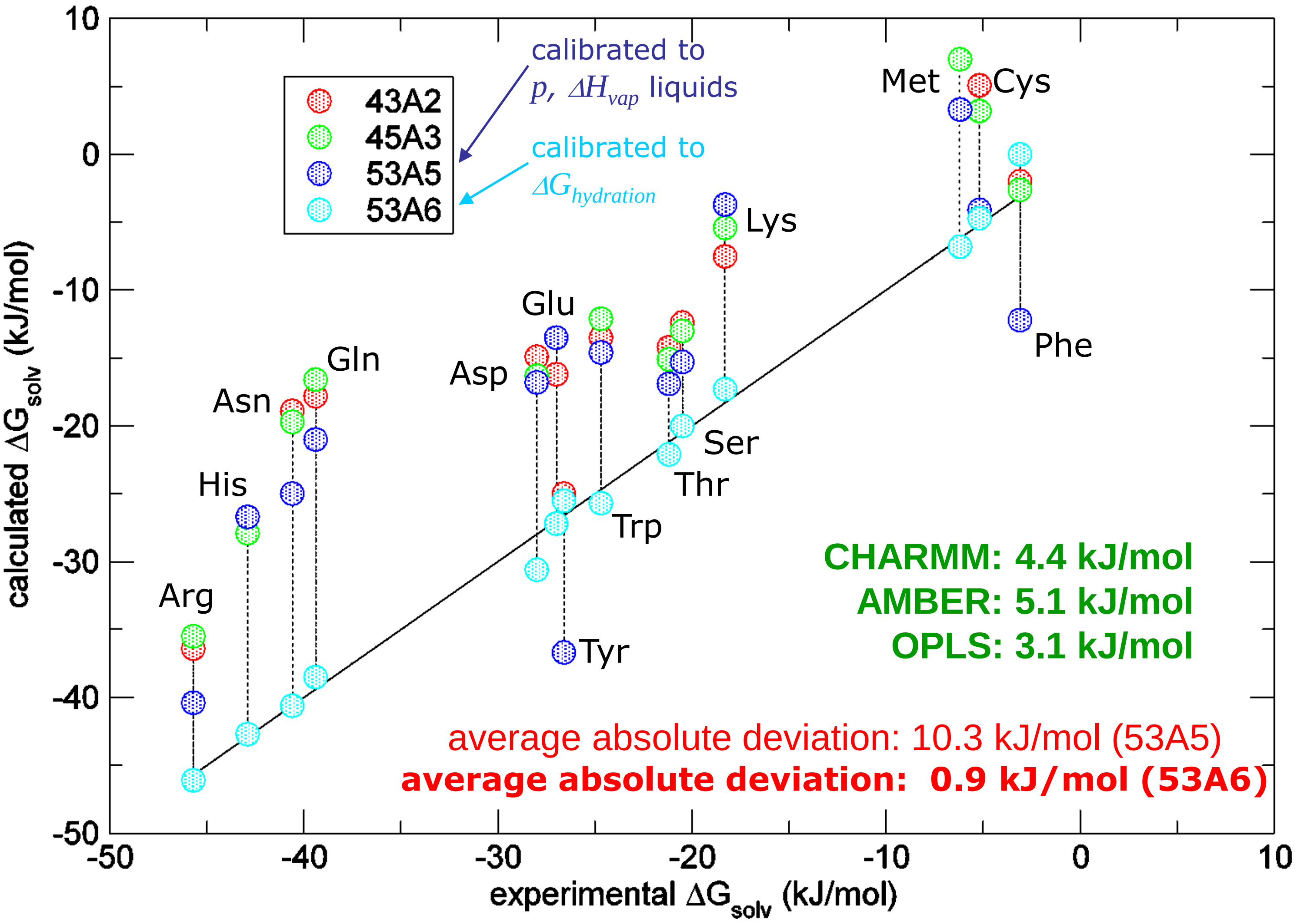


average absolute deviation: 2.2 kJ/mol (53A5 / 53A6)

*Oostenbrink et al., J Comput. Chem. 25 (**2004**) 1656-1676*

Free energy of solvation in water

amino acid analogues (polar)



calibrated to p, ΔH_{vap} liquids

calibrated to $\Delta G_{hydration}$

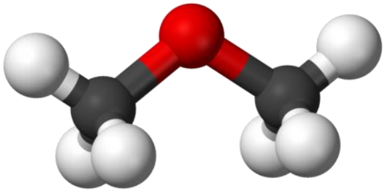
CHARMM: 4.4 kJ/mol
AMBER: 5.1 kJ/mol
OPLS: 3.1 kJ/mol

average absolute deviation: 10.3 kJ/mol (53A5)

average absolute deviation: 0.9 kJ/mol (53A6)

*Oostenbrink et al., J Comput. Chem. 25 (**2004**) 1656-1676*

Use of polarisable force fields



A polarisable force field for dimethyl ether, cyclohexane and water

	pure DME	*1 DME in cyclohexane*	*1 DME in water*
	ΔH_{vap} [kJ mol^{-1}]	ΔG_{solv} [kJ mol^{-1}]	ΔG_{hydr} [kJ mol^{-1}]
Experiment	21.7	~ –9.5	~ –7.6
$DME_{nonpol}/solv_{nonpol}$	21.3	–9.3	–3.2
$DME_{pol}/solv_{nonpol}$	21.0	–8.3	–9.6
$DME_{pol}/solv_{pol}$	21.0	–9.9	–7.0

Non-polarisable force field has difficulty reproducing solvation in ***non-polar* and *polar*** solvent.

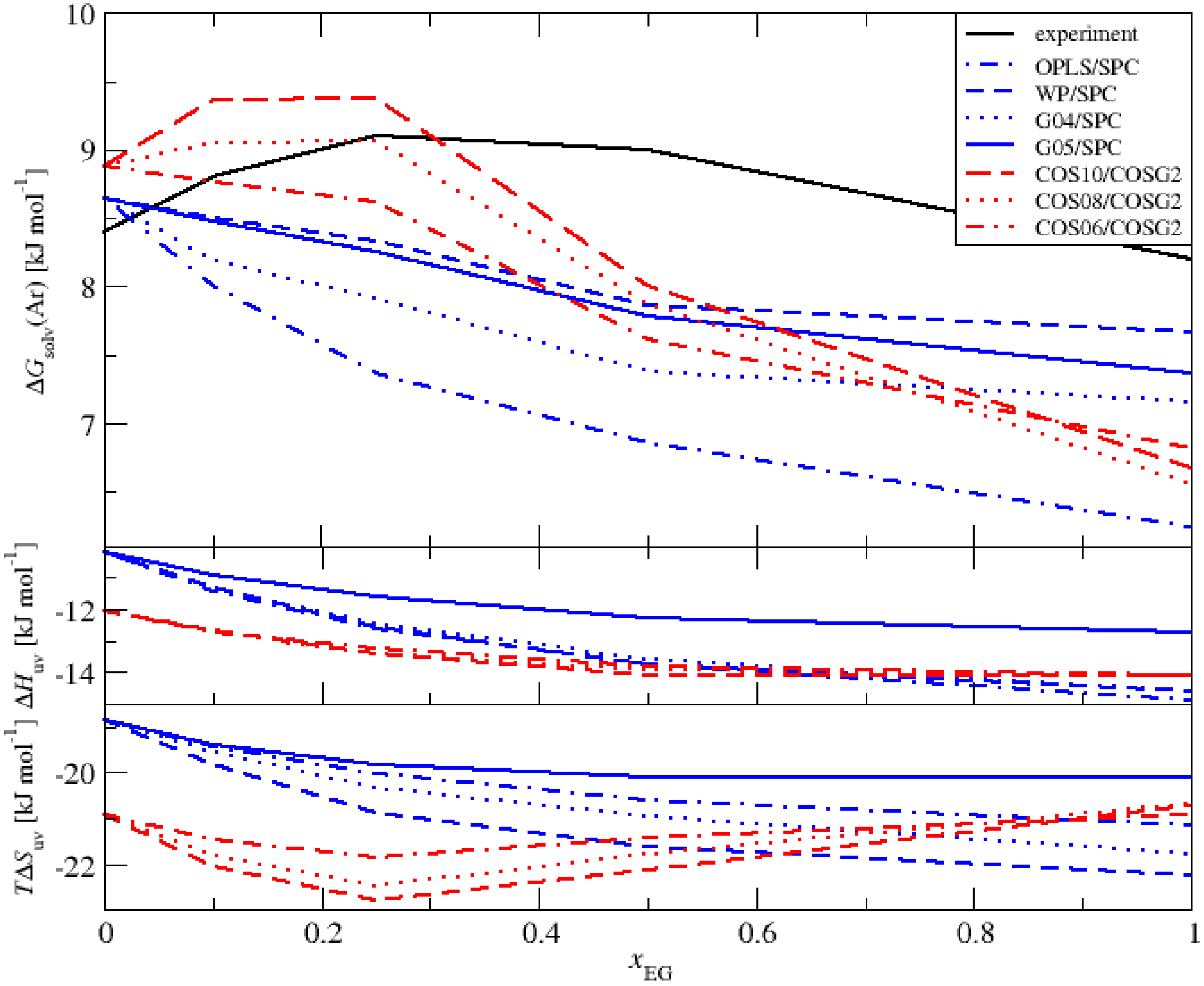
Polarisable DME improves the solvation in ***water***, but degrades solvation in ***cyclohexane***.

Polarisable solvent increases the **transferability** between different environments further.

*Geerke & van Gunsteren, J Phys. Chem. B 111 (**2007**) 6425-6436*

Hydrophobic hydration (argon) in water-ethylene-glycol mixtures

Non-polarisable models versus polarisable models



Free enthalpy
of solvation

Solute-solvent
enthalpy
of solvation

Solute-solvent
entropy
of solvation

Black: experiment

Only polarisable models reproduce the experimental trend

*Geerke & van Gunsteren, Mol. Phys. 105 (**2007**) 1861-1881*

Inclusion of polarisability in molecular models

A. Why polarisability ?

  1. **Effects of polarisability**
  2. **Limitations of non-polarisable force fields**

B. Six aspects

  1. **Definition, distinctions, approximations**

C. Charge-on-spring (COS) models

Accounting for polarisation in molecular simulation

Polarisation

Change the *multipole moments* $\mu^{(n)}$ of a charge distribution due to an (applied) *electric field* $\vec{E}$

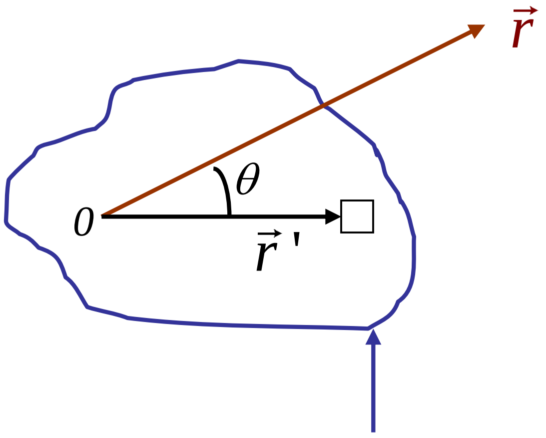
monopole:	charge q	of charge distribution
dipole:	dipole $\vec{\mu}$	
quadrupole:	…	
octupole:	…	

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Potential and field of a charge distribution

Coulomb potential

$$\varphi(\vec{r}) = \frac{1}{4\pi\varepsilon_0}\int \frac{\rho(\vec{r}\,')}{|\vec{r}-\vec{r}\,'|}d\vec{r}\,'$$



$\rho(\vec{r}\,')$ = charge density

Series expansion of the integrand

$$\frac{1}{|\vec{r}-\vec{r}\,'|} = \left[(x-x')^2+(y-y')^2+(z-z')^2\right]^{-\frac{1}{2}}$$

$$= \left[x^2+y^2+z^2-2(xx'+yy'+zz')+x'^2+y'^2+z'^2\right]^{-\frac{1}{2}}$$

$$= \left[r^2-2\vec{r}\cdot\vec{r}\,'+r'^2\right]^{-\frac{1}{2}}$$

$$= \frac{1}{r}\left[1-\frac{2\vec{r}\cdot\vec{r}\,'}{r^2}+\left(\frac{r'}{r}\right)^2\right]^{-\frac{1}{2}}$$

$= \text{ assume } |\vec{r}\,'| \ll |\vec{r}|$ and use $[1+x]^{-\frac{1}{2}} = 1-\frac{1}{2}x+\frac{3}{8}x^2-\frac{5}{16}x^3+\ldots$

Potential and field of a charge distribution

Series expansion of the integrand

$$\frac{1}{\left|\vec{r}-\vec{r}\,'\right|}=\frac{1}{r}\left[1+\frac{\vec{r}\cdot\vec{r}\,'}{r^2}\underbrace{-\frac{1}{2}\left(\frac{r'}{r}\right)^2+\frac{3}{2}\frac{\left(\vec{r}\cdot\vec{r}\,'\right)^2}{r^4}}-\frac{3}{2}\frac{\left(\vec{r}\cdot\vec{r}\,'\right)\vec{r}\,'^2}{r^4}+\frac{3}{8}\left(\frac{r'}{r}\right)^4\dots\right]$$

I	II	III	IV
1	$\frac{r'}{r}$	$\left(\frac{r'}{r}\right)^2$	$\left(\frac{r'}{r}\right)^3$

Term I: monopole

$$\varphi^{I}\left(\vec{r}\right)=\frac{1}{4\pi\varepsilon_0}\frac{1}{r}\int\rho\left(\vec{r}\,'\right)d\vec{r}\,'=\frac{1}{4\pi\varepsilon_0}\frac{q}{r}$$

q = charge

Term II: dipole

$$\varphi^{II}\left(\vec{r}\right)=\frac{1}{4\pi\varepsilon_0}\frac{\vec{r}}{r^3}\cdot\int\vec{r}\,'\rho\left(\vec{r}\,'\right)d\vec{r}\,'=\frac{1}{4\pi\varepsilon_0}\frac{\vec{\mu}\cdot\vec{r}}{r^3}$$

μ = dipole-moment

Term III: quadrupole

$$\varphi^{III}\left(\vec{r}\right)=\frac{1}{4\pi\varepsilon_0}\frac{1}{r^3}\int\frac{1}{2}\left[3\cos^2\theta-1\right]r'^2\,\rho\left(\vec{r}\,'\right)d\vec{r}\,'$$

$$=\frac{1}{4\pi\varepsilon_0}\frac{Q\left(\theta\right)}{r^3}$$

Q = quadrupolemoment

Potential and field of a charge distribution

Electric field

differentiate φ with respect to $\vec{r}$, take minus sign:

Term I: $$E^{I}\left(\vec{r}\right)=\frac{1}{4\pi\varepsilon_0}\frac{q}{r^2}\frac{\vec{r}}{r}=\frac{q\vec{r}}{4\pi\varepsilon_0 r^3}$$

Term II: $$E^{II}\left(\vec{r}\right)=\frac{1}{4\pi\varepsilon_0}\left[-\frac{\vec{\mu}}{r^3}+\frac{3\vec{r}\left(\vec{\mu}\cdot\vec{r}\right)}{r^5}\right]=\underbrace{\frac{1}{4\pi\varepsilon_0}\frac{1}{r^3}\left[\frac{3\vec{r}\vec{r}}{r^2}-1\right]}_{\text{dipole tensor } \overleftrightarrow{T}}\cdot\vec{\mu}$$

Macroscopic description of polarisation

Continuum with relative dielectric permittivity ε_r

or susceptibility χ

- **dielectric displacement:** $\vec{D} = \varepsilon_0 \varepsilon_r \vec{E}$

- **polarisation:** $\vec{P} = (\varepsilon_r - 1)\varepsilon_0 \vec{E} = \chi \vec{E}$

- **Coulomb energy:** $U(r_i, r_j) = \frac{1}{4\pi\varepsilon_0\varepsilon_r} \frac{q_i q_j}{|r_i - r_j|}$

Accounting for polarisation in molecular simulation

Distinguish:

1. **Dipole** moment versus other **multipole** moments
   - monopole generally does not change (charge conservation)
   - dipole term then dominates expansion

2. **Homogeneous** versus ***in*homogenous** fields

$\vec{E} = \vec{E}\left(\vec{r}\right)$ $\quad$ $\vec{E}$ varies with $\vec{r}$

3. **Linear** versus **non-linear** dependence of induced moment on field $\vec{E}$

$\vec{\mu} = \overleftrightarrow{\alpha}\vec{E}$ $\quad$ $\vec{\mu} = \vec{f}\left(\vec{E}\right)$

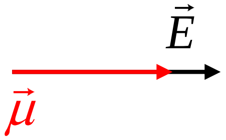
*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Accounting for polarisation in molecular simulation

Distinguish:

4. **Isotropic** versus ***an*isotropic** polarisation

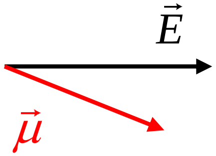
$\vec{\mu} = \alpha \vec{E}$



$\alpha = \text{scalar}$

$\vec{\mu}$ in direction of field $\vec{E}$

$\vec{\mu} = \overleftrightarrow{\alpha} \vec{E}$



$\overleftrightarrow{\alpha}$ is a tensor

5. **Permanent** dipoles versus **induced** dipoles
gas phase
due to surroundings in the condensed phase

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Various approximations used

1. **linear dipole** polarisation in a ***non*-homogeneous electric field**

$$\vec{\mu}\left(\vec{E}\right) = \overleftrightarrow{\alpha}\vec{E} + \underbrace{\frac{1}{3}\overleftrightarrow{\alpha}'\vec{\nabla}\vec{E} + \frac{1}{15}\overleftrightarrow{\alpha}''\vec{\nabla}\vec{\nabla}\vec{E}}_{\text{non-uniform part, neglected in homogeneous field approximation}} + \ldots$$

2. **linear dipole** polarisation in a **homogeneous electric field**

$$\vec{\mu}\left(\vec{E}\right) = \overleftrightarrow{\alpha}\vec{E}$$

3. ***non*-linear dipole** polarisation in a **homogeneous electric field**

$$\vec{\mu}\left(\vec{E}\right) = (\overleftrightarrow{\alpha} + \underbrace{\overleftrightarrow{\beta}\vec{E} + \frac{1}{2}\overleftrightarrow{\gamma}\vec{E}\vec{E} + \ldots}_{\text{non-linear part, neglected in linear response approximation}})\ \vec{E}$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Various approximations used

4. **isotropic linear dipole** polarisation in a **homogeneous field**

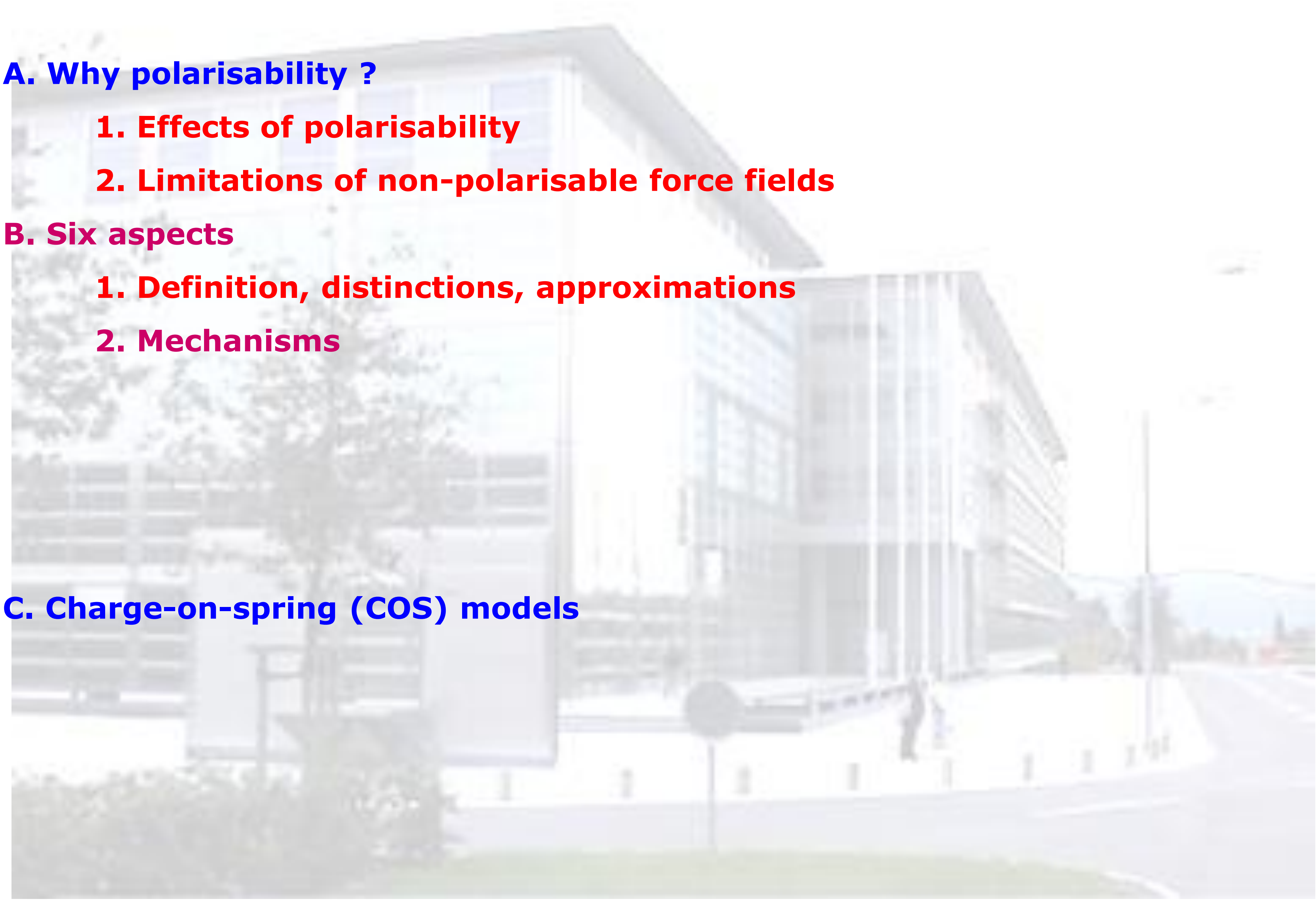
$$\begin{pmatrix}\mu_x\\ \mu_y\\ \mu_z\end{pmatrix} = \underbrace{\begin{pmatrix}\alpha_{xx} & \alpha_{xy} & \alpha_{xz}\\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz}\\ \alpha_{zx} & \alpha_{zy} & \alpha_{zz}\end{pmatrix}}_{\text{tensor character, neglected in isotropic polarization approximation}} \begin{pmatrix}E_x\\ E_y\\ E_z\end{pmatrix} \longrightarrow \begin{pmatrix}\mu_x\\ \mu_y\\ \mu_z\end{pmatrix} = \underset{\substack{\uparrow\\ \textit{scalar}}}{\alpha} \begin{pmatrix}E_x\\ E_y\\ E_z\end{pmatrix}$$

5. **no** (explicit) **induced dipoles**

$$\underset{\substack{\uparrow\\ \text{may include mean polarisation}}}{\vec{\mu}}{}^{\text{permanent}} \neq \vec{0} \qquad \underbrace{\vec{\mu}^{\text{induced}}\left(\vec{E}\right) = \vec{0}}_{\text{neglect of induced polarisation}}$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Inclusion of polarisability in molecular models



A. Why polarisability ?

1. Effects of polarisability

2. Limitations of non-polarisable force fields

B. Six aspects

1. Definition, distinctions, approximations

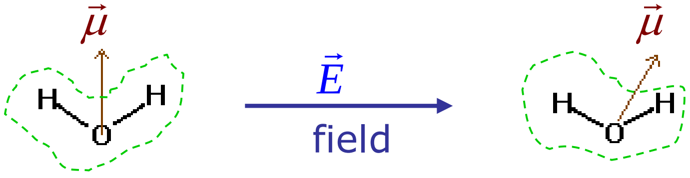
2. Mechanisms

C. Charge-on-spring (COS) models

Molecular mechanisms of polarisation

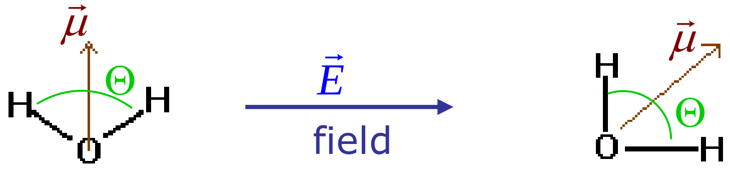
1. **Electronic:** ***redistribution of electrons*** over atoms/molecules
2. **Geometric:** ***change of geometry*** of a molecule
3. **Orientational:** ***realignment*** of molecule

Ad 1:



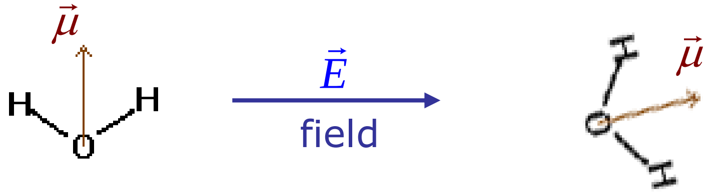
electron density shifts to left due to $\vec{E}$

Ad 2:



bond angle Θ narrows due to $\vec{E}$

Ad 3:



molecular orientation changes due to $\vec{E}$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Inclusion of polarisability in molecular models

A. Why polarisability ?

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1. Definition, distinctions, approximations
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3. Three types of treatments

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Modelling of polarisability in molecular simulation

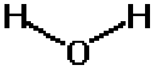
1. Mean-field models:

implicit polarisation

permanent dipole moment of a molecule is **enhanced** from gas phase value to the condensed phase value

for example:

μ_{gas} = 1.85 Debye

water  μ_{SPC} = 2.27 Debye

SPC (simple point charge) model for ***liquid*** water

good model for homogeneous environment,
but not for *in*homogeneous surroundings

→ H_2O bound to protein or ion or in a membrane

Modelling of polarisability in molecular simulation

2. Explicit, classical polarisation in the molecular model

Introduction of *inducible dipoles* in molecules

- **more expensive**
- **not easy to parameterise**

3. Quantum-mechanical treatment of electronic degrees of freedom

The electron density can be polarised

- **not efficient for condensed phase systems**
  e.g. ionic solutions

Inclusion of polarisability in molecular models

A. Why polarisability ?

1. Effects of polarisability
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B. Six aspects

1. Definition, distinctions, approximations
2. Mechanisms
3. Three types of treatments
4. Three types of models, choices to be made, considerations

C. Charge-on-spring (COS) models

How to introduce classical, explicit polarisability into molecular models for simulation

A. Generating induced dipoles: 3 methods

1. induced *point* dipoles $\vec{\mu}_i$ at sites $\vec{r}_i$

$$\vec{\mu}_i = \alpha_i \vec{E}\left(\vec{r}_i\right)$$

2. changing* the *size* of the (atomic) *charges

q_j at $\vec{r}_j$ such that $\vec{\mu}_i = \sum_j \Delta q_j \vec{r}_j = \alpha_i \vec{E}\left(\vec{r}_i\right)$

so-called **fluctuation-charge models**

3. changing* the *geometry* of the *charge distribution, e.g. by changing the position of virtual charge q_j^{υ} such that

$$\vec{\mu}_i = \sum_j q_j^{\upsilon} \vec{r}_j^{\,\upsilon} = \alpha_i \vec{E}\left(\vec{r}_i\right)$$

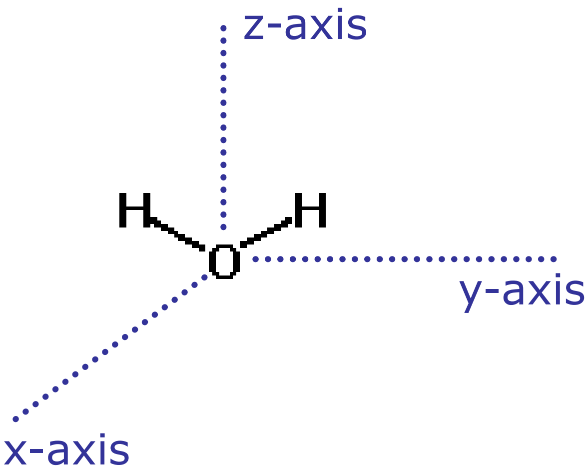
for example: **charge-on-spring model (COS)**

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

How to introduce classical, explicit polarisability into molecular models for simulation

B. Choice of isotropic or anisotropic polarisation

$$\begin{pmatrix} \mu_x \\ \mu_y \\ \mu_z \end{pmatrix} = \begin{pmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{zx} & \alpha_{zy} & \alpha_{zz} \end{pmatrix} \begin{pmatrix} E_x \\ E_y \\ E_z \end{pmatrix}$$



Water

$$\left.\begin{aligned} \alpha_{xx} &= 1.415\ (4\pi\varepsilon_0)10^{-3}\mathrm{nm}^3 \\ \alpha_{yy} &= 1.528\ (4\pi\varepsilon_0)10^{-3}\mathrm{nm}^3 \\ \alpha_{zz} &= 1.468\ (4\pi\varepsilon_0)10^{-3}\mathrm{nm}^3 \end{aligned}\right\}\ \alpha = 1.47\ (4\pi\varepsilon_0)10^{-3}\mathrm{nm}^3$$

off-diagonal elements experimentally not known

bulk of polarisation effect is captured using *isotropic* polarisation

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

How to introduce classical, explicit polarisability into molecular models for simulation

C. Choosing the sites of the induced dipoles

- **on atoms of model**
- **on other sites:**
  - on bonds (bond polarisability)
  - on virtual atoms

this may introduce torques

D. Avoid the polarisation catastrophe

If two **inducible dipoles** come spatially **too close to each other**, the dipolar interaction between them mutually **enhances their *induced dipoles to infinity***

for example: water $r_{\mathrm{OO}} \geq \left[4\alpha^2 / (4\pi\varepsilon_0)^2 \right]^{\frac{1}{6}} \approx 0.144 \text{ nm}$

Remedies:

- damp polarisability at short distances
- **use non-linear polarisation, e.g.** $\mu = \underset{\uparrow}{\alpha} \ln\left(E+1\right)$ *sublinear*
- use smaller, more distributed polarisabilities

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Considerations regarding choice of model to represent induced dipoles

Accuracy versus simplicity

1. **no induced multipoles beyond dipoles**

   forces are already 3-rd rank tensors using point dipoles

2. **monopoles (charges) are most easy to handle in schemes to compute long-range electrostatic forces**

   particle-mesh schemes, virial

   so: fluctuation-charge or charge-on-spring models

3. **rather no rigid virtual sites**
   no anisotropy

   } may result in torques

4. **fluctuation charge models**

   ***scaling the charges** of a charge distribution*
   does change all multipoles in a fixed ratio

5. **charge-on-spring models**

   if q_j^{ν} is large, separation $\vec{r}_j^{\,\nu}$ is small
   ***dipole approximation is good**, so, other multipoles don't change*

The charge-on-spring models are the *simplest* realisations of polarisation

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

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2. Limitations of non-polarisable force fields

B. Six aspects

1. Definition, distinctions, approximations
2. Mechanisms
3. Three types of treatments
4. Three types of models, choices to be made, considerations
5. Expressions for the energy and forces (point dipoles)

C. Charge-on-spring (COS) models

Induced point dipoles: expression for the energy

Induced dipoles:

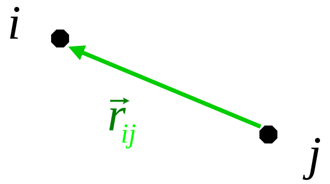
at sites of i=1,2 ... N atoms with permanent charges q_i

$$\vec{\mu}_i = \alpha_i \vec{E}_i = \alpha_i \left\{ \vec{E}_i^{\,q} + \sum_{\substack{j=1\\ j\neq i}}^{N} \overleftrightarrow{T}_{ij}\,\vec{\mu}_j \right\}$$

$$\underline{M} = \underline{A}\left[\,\underline{E}^{\,q} + \underline{T}\,\underline{M}\,\right]$$

Electrostatic field from permanent charges:

$$\vec{E}_i^{\,q} = \sum_{\substack{j=1\\ j\neq i}}^{N} \frac{1}{4\pi\varepsilon_0}\,\frac{q_i\vec{r}_{ij}}{r_{ij}^3}$$



Dipole tensor:

$$\overleftrightarrow{T}_{ij} = \frac{1}{4\pi\varepsilon_0}\,\frac{1}{r_{ij}^3}\left[\frac{3\vec{r}_{ij}\vec{r}_{ij}}{r_{ij}^2} - 1\right]$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Induced point dipoles: expression for the energy

Electrostatic energy:

$$U_{el} = U_{qq} + U_{ind} = U_{qq} + U_{stat} + U_{\mu\mu} + U_{self}$$

$$U_{qq} = \frac{1}{2} \sum_{i=1}^{N} \sum_{\substack{j=1 \\ j \neq i}}^{N} \frac{1}{4\pi\varepsilon_0} \frac{q_i q_j}{r_{ij}}$$

$$U_{stat} = -\sum_{i=1}^{N} \vec{\mu}_i \cdot \vec{E}_i^{q}$$

$$U_{\mu\mu} = -\frac{1}{2} \sum_{i=1}^{N} \sum_{\substack{j=1 \\ j \neq i}}^{N} \vec{\mu}_i \overset{\leftrightarrow}{T}_{ij} \vec{\mu}_j$$

$$U_{self} = \sum_{i=1}^{N} \int_0^{\vec{\mu}i} \vec{E}_i \cdot d\vec{\mu}_i^{'} = \sum_{i=1}^{N} \int_0^{\vec{\mu}i} \frac{\vec{\mu}_i^{'}}{\alpha_i} d\vec{\mu}_i^{'} = \sum_{i=1}^{N} \frac{\vec{\mu}_i^{2}}{2\alpha_i}$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Induced point dipoles: expression for the forces

At equilibrium:

$$\frac{\partial U_{el}}{\partial \vec{\mu}_i} = 0 \quad \text{or} \quad \vec{\mu}_i = \alpha_i \vec{E}_i$$

Force is the negative gradient of U_{el}:

$$\vec{f}_k = -\frac{\partial U_{el}}{\partial \vec{r}_k} - \sum_{i=1}^{N} \frac{\partial U_{el}}{\partial \vec{\mu}_i} \cdot \frac{\partial \vec{\mu}_i}{\partial \vec{r}_k} \qquad \frac{\partial U_{el}}{\partial \vec{\mu}_i} = 0$$

$$= -\frac{\partial}{\partial \vec{r}_k}[\underbrace{U_{qq} + U_{stat} + U_{\mu\mu}}_{\text{only these contribute}} + U_{self}]$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Induced point dipoles: expression for the forces

Force is the negative gradient of U_{el}:

$$\vec{f}_k = q_k \vec{E}_k^q + \sum_{i=1}^{N} \vec{\mu}_i \cdot \frac{\partial \vec{E}_i^q}{\partial \vec{r}_k} + \sum_{\substack{i=1\\ i\neq k}}^{N} \frac{\partial}{\partial \vec{r}_k}\left(\vec{\mu}_i \overleftrightarrow{T}_{ik} \vec{\mu}_k\right)$$

$$= q_k \vec{E}_k^q + \sum_{i=1}^{N} \vec{\mu}_i \cdot \frac{\partial}{\partial \vec{r}_k}\left(\sum_{\substack{j=1\\ j\neq k}}^{N} \frac{1}{4\pi\varepsilon_0}\frac{q_j \vec{r}_{ij}}{r_{ij}^3}\right)$$

$$+ \sum_{\substack{i=1\\ i\neq k}}^{N} \frac{1}{4\pi\varepsilon_0}\frac{3}{r_{ik}^5}\left\{\frac{5}{r_{ik}^2}\left(\vec{\mu}_i\cdot\vec{r}_{ik}\right)\left(\vec{\mu}_k\cdot\vec{r}_{ik}\right)\vec{r}_{ik} - \left(\vec{\mu}_i\cdot\vec{\mu}_k\right)\vec{r}_{ik} - \left(\vec{\mu}_i\cdot\vec{r}_{ik}\right)\vec{\mu}_k - \left(\vec{\mu}_k\cdot\vec{r}_{ik}\right)\vec{\mu}_i\right\}$$

if the induced dipoles $\vec{\mu}_i$ are known, force $\vec{f}_k$ is known

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Inclusion of polarisability in molecular models

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- 2. Limitations of non-polarisable force fields

B. Six aspects

- 1. Definition, distinctions, approximations
- 2. Mechanisms
- 3. Three types of treatments
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- 6. Techniques to solve the field equations

C. Charge-on-spring (COS) models

Equation for the induced dipoles or field equation

Induced dipoles: $\vec{\mu}_i = \alpha_i \vec{E}_i = \alpha_i \left\{ \vec{E}_i^q + \sum_{\substack{j=1 \\ j \neq i}}^{N} \overleftrightarrow{T}_{ij} \vec{\mu}_j \right\}$

Induced dipoles equation: $\vec{\mu}_i = \alpha_i \left\{ \vec{E}_i^q + \sum_{\substack{j=1 \\ j \neq i}}^{N} \overleftrightarrow{T}_{ij} \vec{\mu}_j \right\}$

Field equation: $\vec{E}_i = \left\{ \vec{E}_i^q + \sum_{\substack{j=1 \\ j \neq i}}^{N} \alpha_i \overleftrightarrow{T}_{ij} \vec{E}_j \right\}$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Equation for the induced dipoles or field equation

Using matrix notation:

$$\underline{M} = \begin{pmatrix} \vec{\mu}_1 \\ \\ \\ \vec{\mu}_N \end{pmatrix} \qquad \underline{A} = \begin{pmatrix} \alpha_1 & & & \\ & \alpha_2 & & \\ & & \ddots & \\ & & & \alpha_N \end{pmatrix} \qquad \underline{T} = \text{dipole tensor}$$

$$\underline{T}_{ij} = \frac{1}{4\pi\varepsilon_0} \frac{1}{r_{ij}^3} \left\{ \frac{3}{r_{ij}^2} \begin{pmatrix} x_{ij}x_{ij} & x_{ij}y_{ij} & x_{ij}z_{ij} \\ y_{ij}x_{ij} & y_{ij}y_{ij} & y_{ij}z_{ij} \\ z_{ij}x_{ij} & z_{ij}y_{ij} & z_{ij}z_{ij} \end{pmatrix} - \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \right\}$$

Induced dipole equation:

$$\underline{M} = \underline{A}\underline{E} = \underline{A}\left[\underline{E}^q + \underline{T}\underline{M}\right]$$

or

$$\left[\underline{A}^{-1} - \underline{T}\right]\underline{M} = \underline{E}^q \quad \textbf{so} \quad \underline{M} = \left[\underline{A}^{-1} - \underline{T}\right]^{-1} \underline{E}^q$$

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Methods to solve the field equations or to find the induced dipoles

Four methods

1. **matrix inversion:** invert $\left[\underline{A}^{-1} - \underline{T}\right]$

   3N x 3N matrix → effort proportional to N^3 **expensive**

2. **iterative solution:**

$$\underline{M}^{(n)} = \underline{A}\left[\underline{E}^{q} + \underline{T}\,\underline{M}^{(n-1)}\right] \qquad n = 1, 2, \ldots$$

3. **use a prediction from previous MD steps (plus iteration)**

$$\vec{\mu}_i(t) = 2\vec{\mu}_i(t-\Delta t) - \vec{\mu}_i(t-2\Delta t)$$

efficient method (combined with iteration)

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

Methods to solve field equations or to find the induced dipoles

Four methods

4. Treat $\vec{\mu}_i$ as additional dynamical variables

extended system technique:

Lagrangian such that $\langle \vec{\mu}_i \rangle = \alpha_i \langle \vec{E}_i \rangle$

$$L = \frac{1}{2}\sum_{i=1}^{N} m\,\dot{\vec{r}}_i^{\,2} + \frac{1}{2}\sum_{i=1}^{N} M_i^{\mu}\,\dot{\vec{\mu}}_i^{\,2} - \frac{1}{2}\sum_{i=1}^{N}\sum_{\substack{j=1\\ j\neq 1}}^{N} \frac{1}{4\pi\varepsilon_0}\frac{q_i q_j}{r_{ij}}$$

$$-\sum_{i=1}^{N} \vec{\mu}_i \cdot \vec{E}_i + \sum_{i=1}^{N} \frac{\vec{\mu}_i^{\,2}}{2\alpha_i}$$

Small time step required, fluctuations induce dispersion forces

*Yu & van Gunsteren, Comput. Phys. Commun. 172 (**2005**) 69-85*

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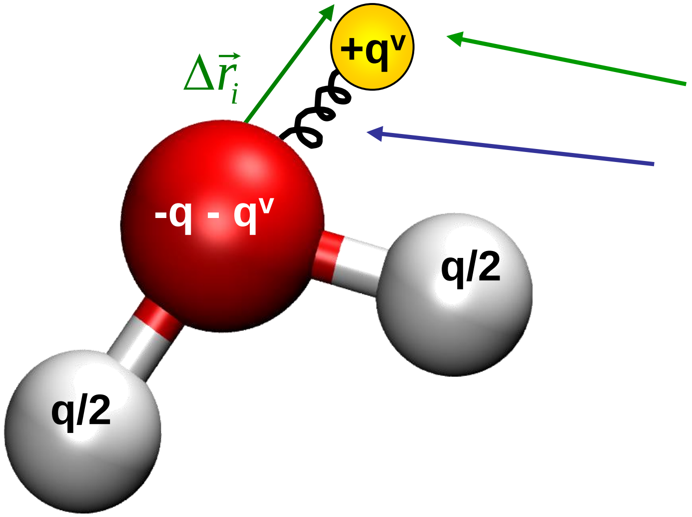
C. Charge-on-spring (COS) models

- **1. Equations, parameters, non-linear polarisation**

The Charge-On-Spring (COS) model

The **simplest realisation of polarisation** is the **displacement** of a **charge** q^v at a **virtual (massless) site** which is **restrained by** a harmonic potential (a **spring**) to one of the real (atomic) sites or to a virtual site. Of course there is no intra-molecular Coulomb interaction.

$$\vec{\mu}_i = q_i^v \Delta\vec{r}_i \qquad \Delta\vec{r}_i = \vec{r}_i^{\,v} - \vec{r}_{\mathrm{O}}$$



virtual site

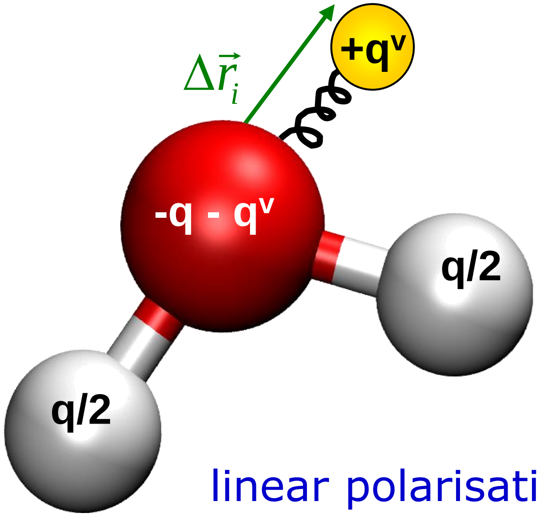
spring force constant $\dfrac{\left(q_i^v\right)^2}{\alpha_i}$

atom polarisability

energy: $U\left(\Delta\vec{r}_i\right) = \frac{1}{2} k_i^{ho} \left(\Delta\vec{r}_i\right)^2$

The Charge-On-Spring Model

The **virtual particle i** with charge q^{ν} must at any time be positioned such that the **total force acting on it is zero**



$$\left.\begin{aligned} \vec{f}_i^{\,\mathrm{ho}} &= -k_{\mathrm{ho}}\Delta\vec{r}_i \\ \vec{f}_i^{\,el} &= q_i^{\nu}\vec{E}_i \end{aligned}\right\} \quad \vec{f}_i^{\,\mathrm{ho}} + \vec{f}_i^{\,el} = 0$$

$$\longrightarrow \quad \left.\begin{aligned} \Delta\vec{r}_i &= \frac{q_i^{\upsilon}}{k_{\mathrm{ho}}}\vec{E}_i \\ \text{induced dipole} \quad \vec{\mu}_i &= q_i^{\nu}\Delta\vec{r}_i \end{aligned}\right\} \quad \vec{\mu}_i = \frac{\left(q_i^{\nu}\right)^2}{k_{\mathrm{ho}}}\vec{E}_i$$

$$\downarrow$$

linear polarisation: $\vec{\mu}_i = \alpha_i\vec{E}_i$ ⟶ **force constant of spring:** $k_{\mathrm{ho}} = \dfrac{\left(q_i^{\nu}\right)^2}{\alpha_i}$

Parameters of the model:

1. **site** *i* of charge on spring
2. q_i^{ν} if chosen large (-8e) then $\Delta\vec{r}_i$ small
3. α_i polarisability

Problems with polarisable force fields

Including polarisation in a force field can lead to **overpolarisation** with effects such as **polarisation catastrophy** and **too large dielectric permittivity**

Some remedies:

A	large enough repulsive van der Waals term	all COS models
B	reduced polarisability	COS/B2, COS/G2
C	virtual COS site	COS/G2, **COS/D2**
D	sublinear dependence on electric field	**COS/D2**
E	several COS sites	expensive
F	screening for short distances	ad hoc

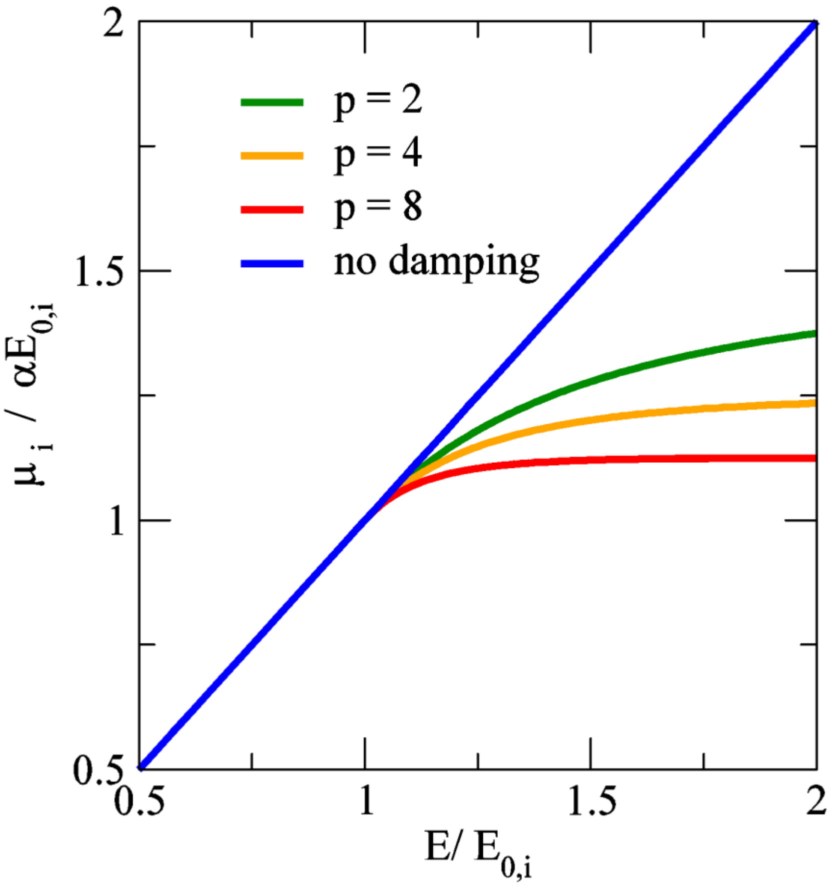
*Yu et al., J. Chem. Phys 118 (**2003**) 221-234*
*Yu & van Gunsteren, J. Chem. Phys 121 (**2004**) 9549-9564*
*Kunz & van Gunsteren, J. Phys. Chem. A113 (**2009**) 11570-11579*
*Bachmann & van Gunsteren, Mol. Phys. 112 (**2014**) 2761-2780*
*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Damped non-linear polarisability

Induced dipole **linear** up to a certain value of the electric field **then levelling off** (saturation).

Continuous and continuous in the **first derivative**:

$$\vec{\mu}_i = \begin{cases} \alpha_i \vec{E}_i & \left|\vec{E}_i\right| < E_{0,i} \\ \dfrac{\alpha_i E_{0,i}}{p}\left[p+1-\left(\dfrac{E_{0,i}}{\left|\vec{E}_i\right|}\right)^p\right]\hat{E}_i & \left|\vec{E}_i\right| \geq E_{0,i} \end{cases}$$



Accounts for hyperpolarisability in a simplified way.

*Kunz & van Gunsteren, J. Phys. Chem. A113 (**2009**) 11570-11579*

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2. Applications: liquid water and other solvents

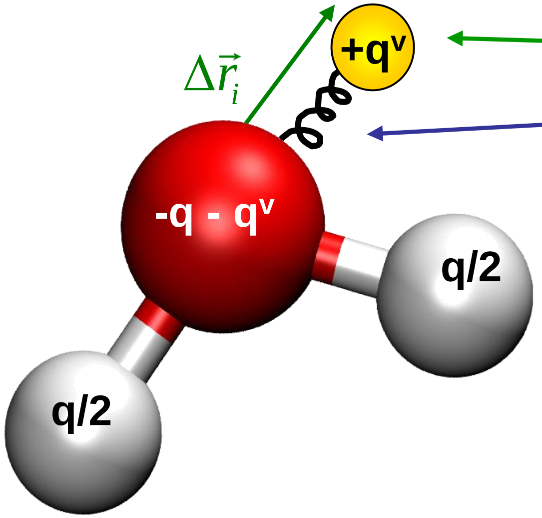
An example of a *sub-atomic* water model: The COS/D2 polarisable model

- ## Four-site (FG) model

The **simplest realisation of polarisation** is the **displacement** of a **charge** q^v at a **virtual (massless) site** which is **restrained by** a harmonic potential (a **spring**) to one of the real (atomic) sites or to a virtual site.

Inducible electric dipole $\vec{\mu}_i = q_i^v \Delta\vec{r}_i$

$$\Delta\vec{r}_i = \vec{r}_i^{\,v} - \vec{r}_{\mathrm{O}}$$



virtual site

spring force constant $\dfrac{\left(q_i^v\right)^2}{\alpha_i}$

atom polarisability

energy: $U\left(\Delta\vec{r}_i\right) = \dfrac{1}{2} k_i^{ho} \left(\Delta\vec{r}_i\right)^2$

*Kunz & van Gunsteren, J. Phys. Chem. A113 (**2009**) 11570-11579*
*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Force-field parameters: water

non-polarisable polarisable

	Exp.	**SPC**	COS/G2	**COS/D2**
C_6 (O-O) (10^{-3} kJmol^{-1}nm^{6})		2.617	3.244	3.2444
C_{12} (O-O) (10^{-6} kJmol^{-1}nm^{12})		2.634	3.458	3.252
C_{12} (H-H) (10^{-6} kJmol^{-1}nm^{12})				3.0
μ_0 (D)	**1.855**	**2.270**	1.850	**1.855**
α ($4\pi\varepsilon_0$ 10^{-3} nm^3)	**1.494**		**1.255**	**1.3**

μ_0 increased **α reduced** **α reduced**

- Geometry: d_{OH} : 0.09572 nm <*HOH*: 104.52°
- Virtual site M: d_{OM} : 0.02472 nm (COS/G2 : 0.022 nm)
- Charge on spring: -8e
- Damping: p : 8 E_0 : 140 (kJmol^{-1}nm^{-3})$^{1/2}$

*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Results: thermodynamic quantities, water

				non-polarisable		polarisable
			Exp	SPC	COS/G2	**COS/D2**
ρ	(kgm^{-3})	density	**997**	**973**	999	999
ΔH_{vap}	(kJmol^{-1})	heat of vaporisation	**44.1**	43.9	43.7	44.1
ΔF_{exc}	(kJmol^{-1})	excess free energy	**24.0**	23.6	21.8	24.3
γ	(mNm^{-1})	surface tension	**71.6**	**48.4**	**59.0**	**63.6**
C_p	(Jmol^{-1}K^{-1})	heat capacity	**75.3**	**93.0**	**107.7**	**88.9**
α_p	(10^{-4} K^{-1})	thermal expansion	**4.22**	**9.0**	**7.0**	4.9
κ_T	(10^{-6} atm^{-1})	compressibility	**45.8**	47.8	47.8	44.4

ρ too small		
γ too small	**γ too small**	**γ too small**
C_p too large	**C_p too large**	**C_p too large**
α_p too large	**α_p too large**	

☐ **parameterised against**

*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Results: dynamic quantities, water

non-polarisable polarisable

	Exp	SPC	COS/G2	**COS/D2**
D (10^{-9} m^{2}s^{-1}) diffusion constant	**2.3**	**4.2**	2.0	2.2
τ_2^{OH} (ps) rotational correlation time	**1.95**	1.9	**3.9**	**3.8**

D **too large** $\boldsymbol{\tau_2^{OH}}$ **too large** $\boldsymbol{\tau_2^{OH}}$ **too large**

*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Results: electric quantities, water

non-polarisable **polarisable**

	Exp.	SPC	COS/G2	**COS/D2**
***ε*(0)** dielectric permittivity	**78.4**	**64.7**	**87.8**	78.9
$<\mu>$ (D) total molecular dipole	2.3 – 2.5	2.27	2.61	2.55
$<\mu^{ind}>$ (D) induced molecular dipole	-	-	0.80	0.73
τ_D (ps) Debye relaxation time	**8.3**	**6.9**	**15.8**	8.4

$\varepsilon(0)$ too small
τ_D too small

$\varepsilon(0)$ too large
τ_D too large

*Bachmann & van Gunsteren, J. Chem. Phys. 141 (**2014**) 22D515*

Properties of non-polarisable and polarisable liquid chloroform $CHCl_3$

Properties	**Experiment**	**Non-polarisable model (G96) 4 sites**	**Polarisable model (COS/C) 5 sites**
ρ (kgm^{-3}) density	**1489**	**1504**	**1489**
ΔH_{vap} $(kJmol^{-1})$ heat of vaporisation	**33.4**	**31.2**	**33.3**
ΔF_{exc} $(kJmol^{-1})$ excess free energy	**15.3**	**15.1**	**16.6**
γ $(10^{-3}\,Nm^{-1})$ surface tension	**27.2**	**25.8**	**28.7**
C_V $(Jmol^{-1}K^{-1})$ heat capacity	**74.7**	**71.7**	**73.5**
α_p $(10^{-3}\,K^{-1})$ thermal expansion	**1.26**	**1.44**	**1.29**
κ_T $(10^{-10}\,Pa^{-1})$ compressibility	**9.98**	**14.2**	**9.2**
$\boldsymbol{\varepsilon}(0)$ dielectric permittivity $\boldsymbol{\varepsilon}(\infty)$	**4.81**	**2.3**	**3.7** **1.2**
τ_D (ps) Debye relaxation time	**5.4**	**4.3**	**5.6**
D $(10^{-9}\,m^2s^{-1})$ diffusion	**2.3**	**2.4**	**2.2**
η (cP) viscosity	**0.56**	**0.48**	**0.55**

Overall "better" model

☐ **parametrised against**

*Z. Lin et al., Mol. Phys. 108 (**2010**) 1749-1757*
*I.G. Tironi & WFvG, Mol Phys. 83 (**1994**) 381-403*

Properties of non-polarisable and polarisable liquid *CCl_4*

Properties	**Experiment**	**Non-polarisable model (G96)** **4 sites** **(smaller system)**	**Polarisable model (COS/C)** **5 sites** **(longer simulation)**
ρ (kgm^{-3}) density	**1594**	**1601**	**1600**
ΔH_{vap} ($kJmol^{-1}$) heat of vaporisation	**32.4**	**32.4**	**32.4**
ΔF_{exc} ($kJmol^{-1}$) excess free energy	**16.3**	**15.8**	**15.8**
γ ($10^{-3}\ Nm^{-1}$) surface tension	**26.8**	**28.8**	**28.8**
$\varepsilon(0)$ dielectric permittivity	**2.24**	**1.0**	**2.24**
D ($10^{-9}\ m^2s^{-1}$) diffusion	**1.15**	**1.8**	**1.9**
η (cP) viscosity	**0.96**	**0.88**	**0.88**

Better representation of dielectric response

☐ **parametrised against**

*A.P.E. Kunz et al., Mol. Phys. 109 (**2011**) 365-372*
*I.G. Tironi et al., Mol Sim. 18 (**1996**) 1-11*

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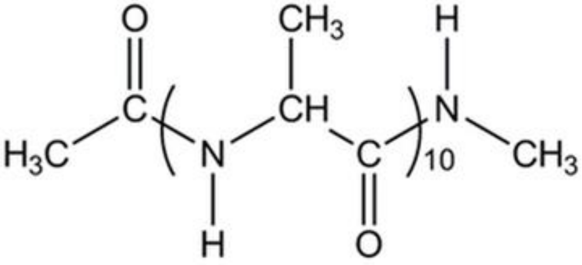
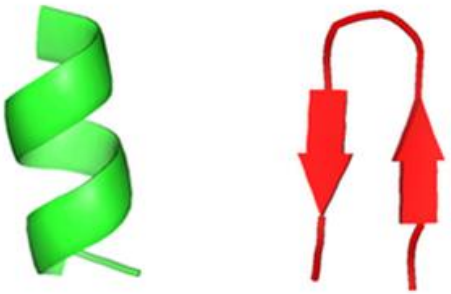
3. Applications: secondary structure preferences of solutes

Stabilisation of α-helical versus β-hairpin secondary structure by polarisability of the solvent

A deca-Ala-peptide in ***water***, ***methanol***, ***chloroform*** or ***CCl_4***

Free enthalpy difference between ***helix*** and ***hairpin*** upon introduction of polarisability into the ***solvent***





Solvent	Free enthalpy difference $(G^{\alpha}_{pol}-G^{\alpha}_{nonpol})-(G^{\beta}_{pol}-G^{\beta}_{nonpol})$ [kJ mol^{-1}]	Per residue [kJmol^{-1}]	Molecular polarisability α [$(4\pi\varepsilon_0)10^{-3}$ nm^3]
water	0.5 ± 3.7	0.0	0.93
methanol	-11.5 ± 3.5	-1.1	1.32
chloroform	-10.2 ± 1.4	-1.0	9.5
CCl4	-21.0 ± 0.6	-2.1	11.1

Polarisability becomes more important for non-polar solvents or environments, e.g. tails of lipids in membranes

*Z. Lin & WFvG, J. Chem. Theory Comput. 11 (**2015**) 1983-1986*

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Accounting for polarisation effects in bio-molecular simulation

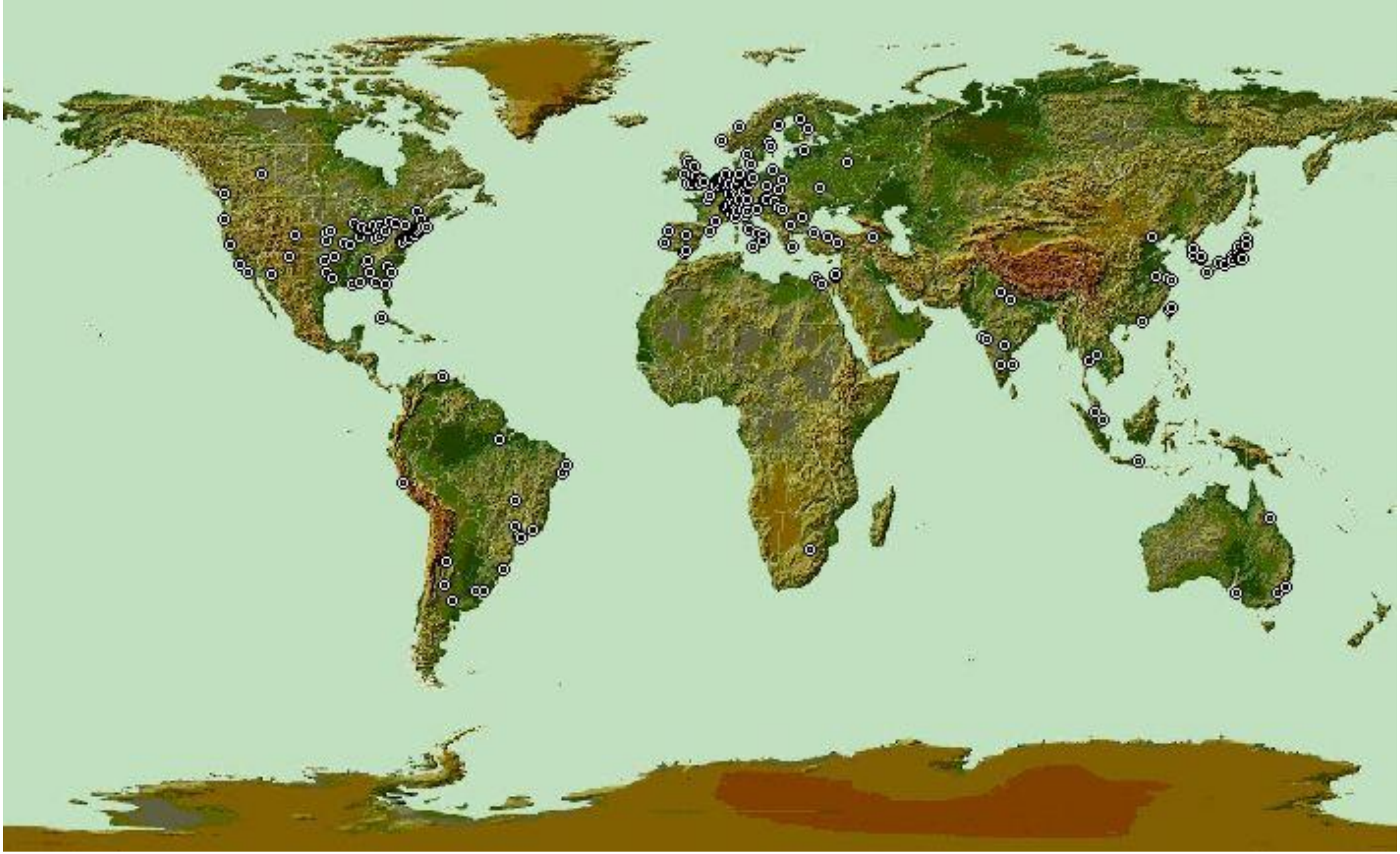
For bio-molecular solutes: proteins, DNA, RNA, ...

use quantum-chemical models,
classical polarisability models are too crude
to properly represent the electron redistribution

For solvents and lipids in membranes:

use classical (Charge-On-Spring) models,
quantum-chemical models are too expensive or inaccurate

Spatial distribution of licences
GROMOS biomolecular simulation software



GROMOS = Groningen Molecular Simulation + GROMOS Force Field

Generally available: http://www.gromos.net