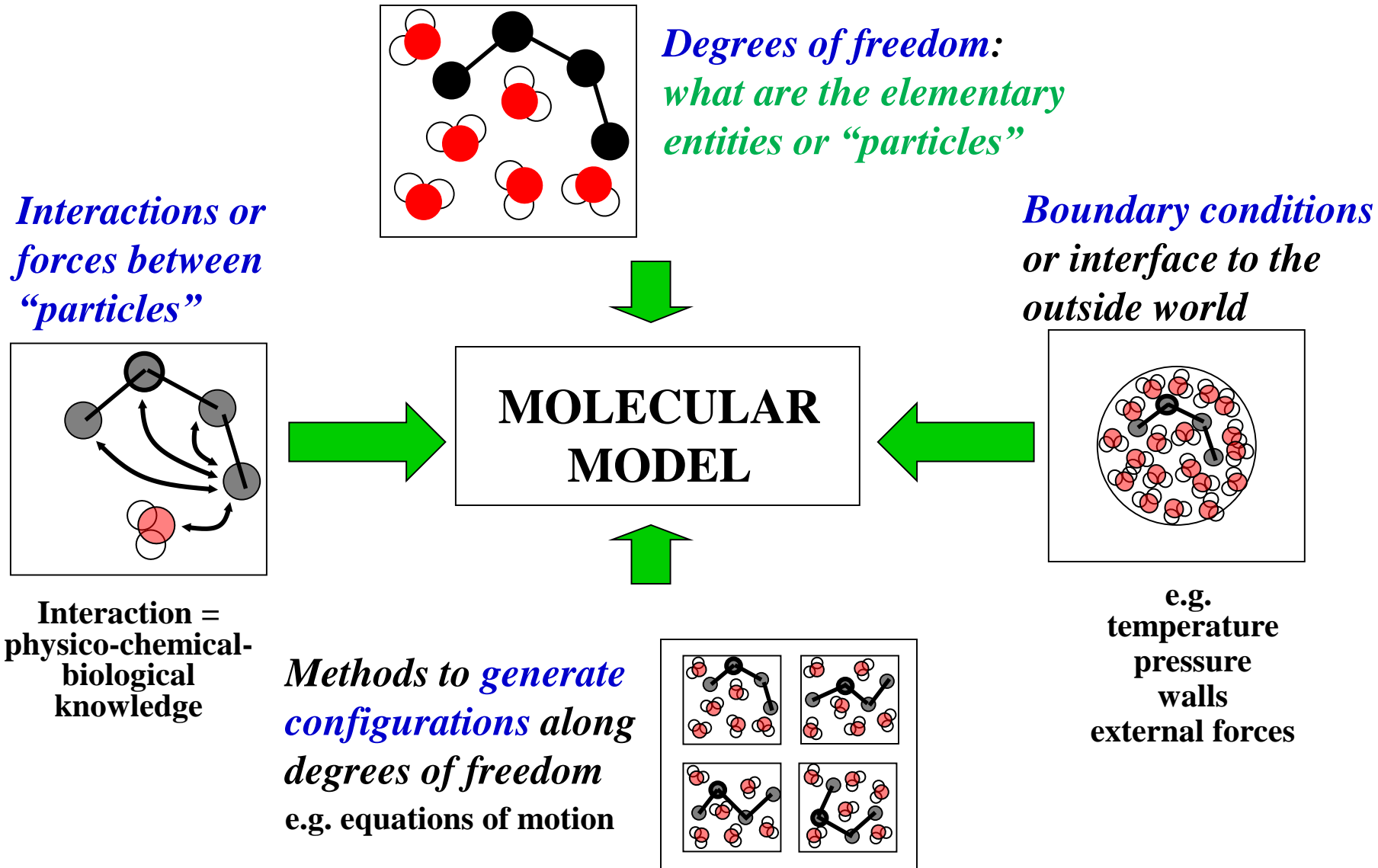# Multi-resolution simulation: methodological issues and applications

Prof. Dr. Wilfred F. van Gunsteren

ETH Zürich, Switzerland

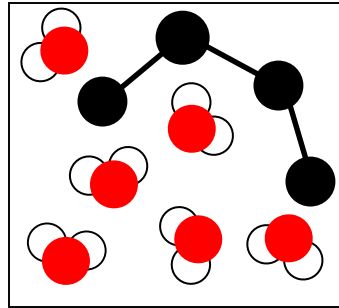# Definition of a model for a computer simulation

For any system *four choices* have to be made

Degrees of freedom:
what are the elementary
entities or "particles"

Interactions or
forces between
"particles"

Boundary conditions
or interface to the
outside world

**MOLECULAR
MODEL**

**Interaction =
physico-chemical-
biological
knowledge**

Methods to generate
configurations along
degrees of freedom
e.g. equations of motion
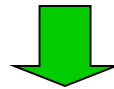
**e.g.
temperature
pressure
walls
external forces**

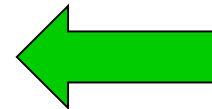# Definition of a model for a computer simulation

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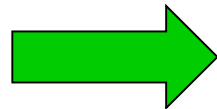
MOLECULAR MODEL

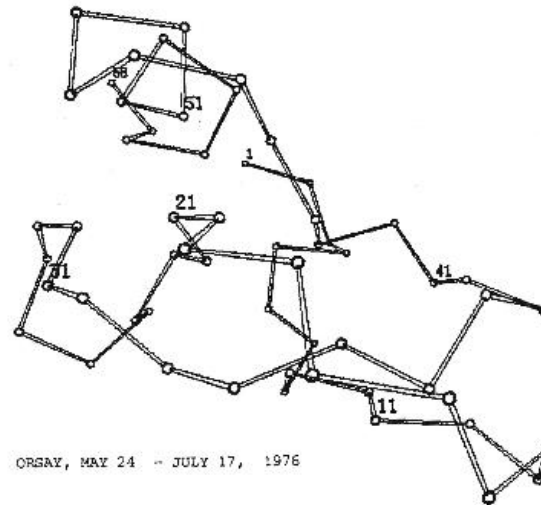# **Protein: Bovine Pancreatic Trypsin Inhibitor (BPTI) in vacuo: *58 particles* (residues) (1976)**

CENTRE EUROPÉEN
DE CALCUL ATOMIQUE ET MOLÉCULAIRE

Bâtiment 506
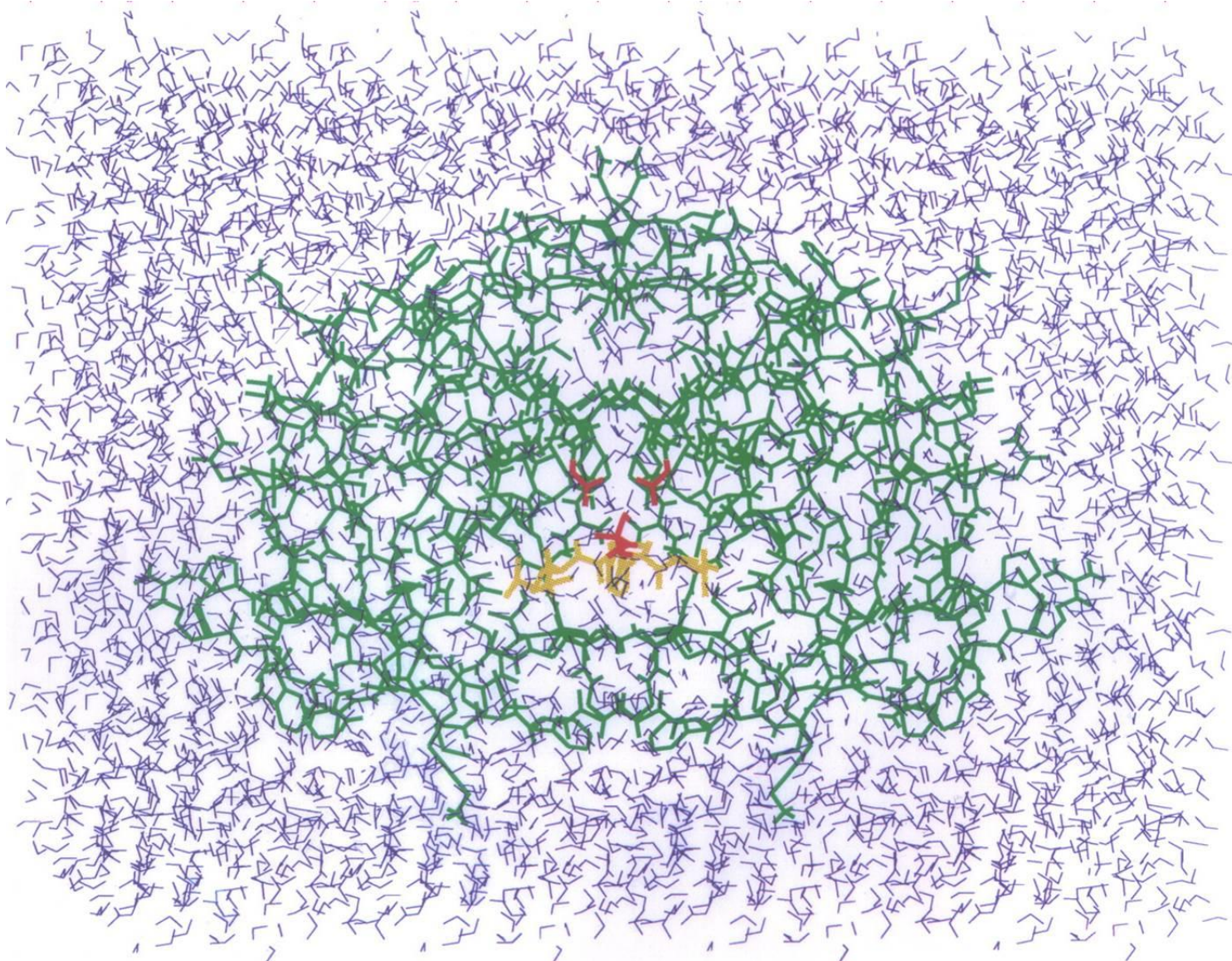UNIVERSITÉ DE PARIS XI
91405 ORSAY, FRANCE

CECAM WORKSHOP

'MODELS FOR PROTEIN DYNAMICS'

ORSAY, MAY 24 – JULY 17, 1976

A rather simple, coarse-grained representation of a protein

Protein: HIV-protease plus inhibitor in water: 21000 atoms (1995)

Different levels of resolution in modelling

Coarse-graining from a *finer-grained* level to a *coarser-grained* level of resolution

Quantum (statistical) mechanics ➡ Classical (statistical) mechanics

Level of resolution	I	II	III	IV	V
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*Riniker et al. Phys. Chem. Chem. Phys. 14 (**2012**) 12423-12430*
*Meier et al., Angew. Chem. Intl. Ed. 52 (**2013**) 2-17*

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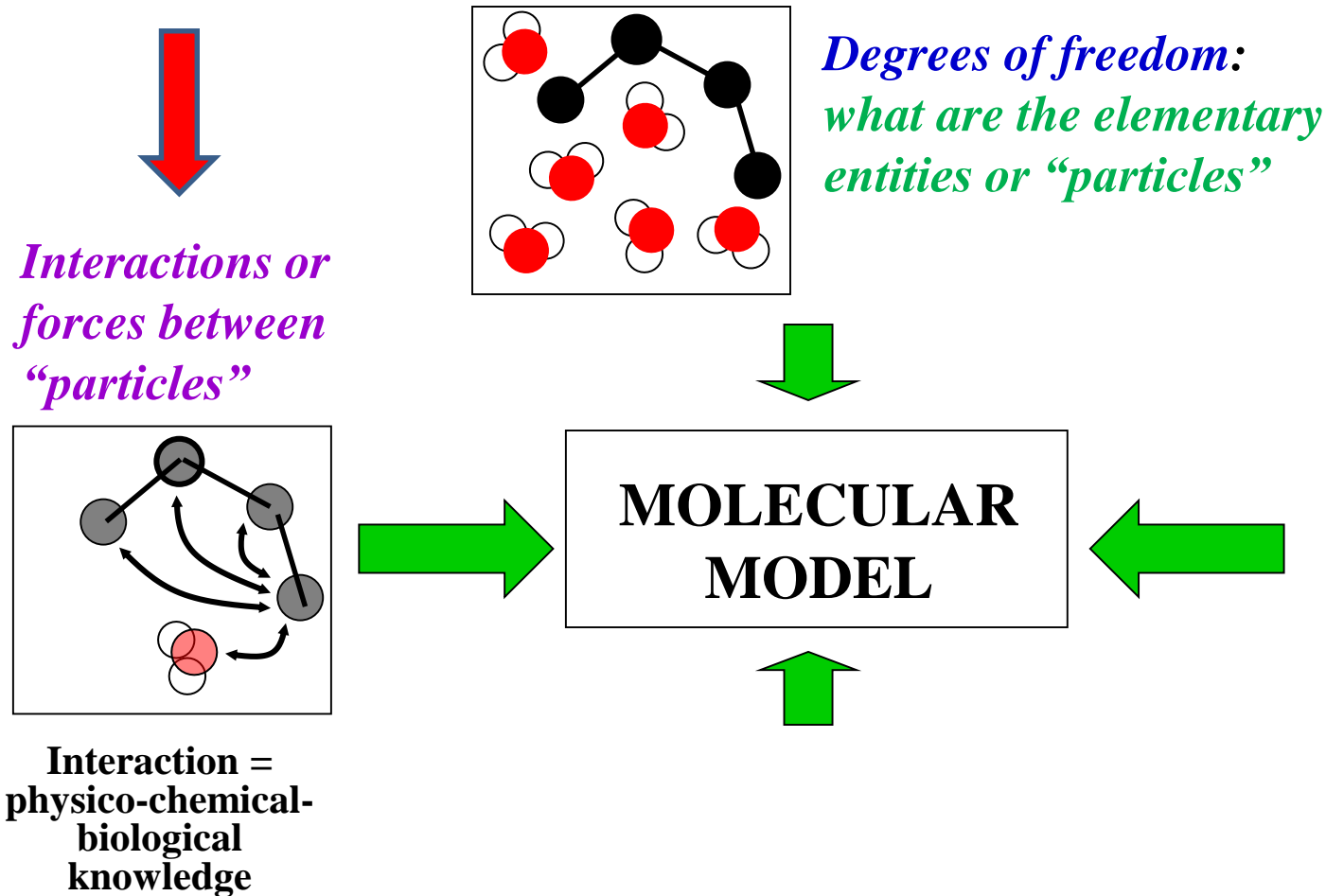*Meier et al., Angew. Chem. Intl. Ed. 52 (**2013**) 2-17*

Main differences between quantum and classical mechanics as applied to molecular systems

Quantum statistical mechanics (QM)	Classical statistical mechanics (CM)
• time-dependent Schrödinger equation: $$i\hbar \frac{\partial \Psi(\vec{r}^N, t)}{\partial t} = \widehat{H}\Psi(\vec{r}^N, t)$$ with wave function Ψ	• Newton's equation: $$\vec{f}_i = m_i\, \vec{a}_i \qquad \vec{f}_i = -\frac{\partial V(\vec{r}^N)}{\partial \vec{r}_i}$$
• Born-Oppenheimer approximation: nuclei and electrons decoupled	• interaction potential energy function $V(\vec{r}^N)$ is generally pair additive, but polarisation can be included
• probabilistic nature of wave function: $$\lvert\Psi(\vec{r}_i, t)\rvert^2,$$ uncertainty principle, no trajectory	• phase space trajectory $\vec{r}^N, \vec{p}^N$
• Bose-Einstein or Fermi-Dirac statistics (Pauli principle)	• Boltzmann statistics

*Meier et al., Angew. Chem. Intl. Ed. 52 (**2013**) 2-17*

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MOLECULAR MODEL

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Quantum (statistical) mechanics → Classical (statistical) mechanics

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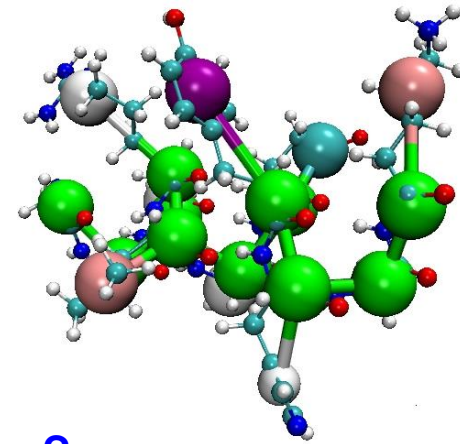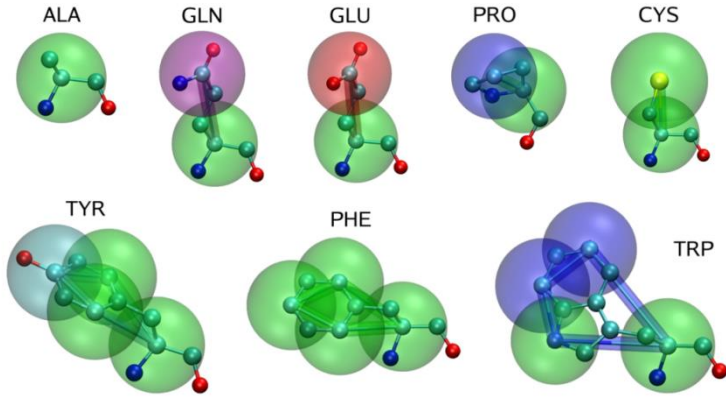_Meier et al., Angew. Chem. Intl. Ed. 52 (**2013**) 2-17_

Modelling involves, at any level of resolution, coarse-graining:

Elimination of non-essential *degrees of freedom* and *interactions* from a more fine-grained level of modelling
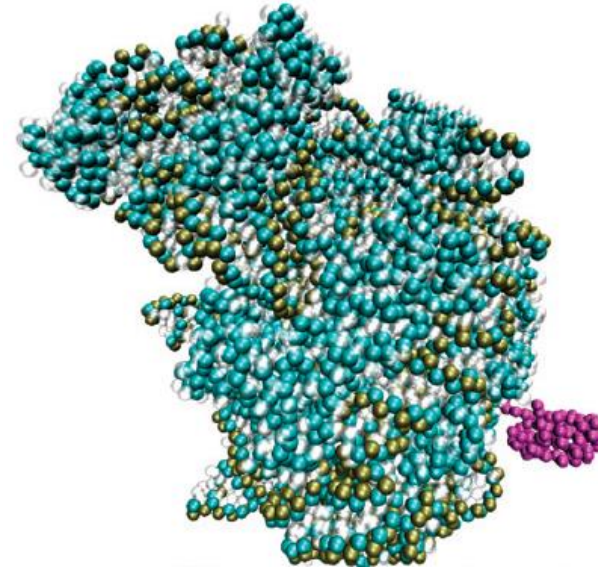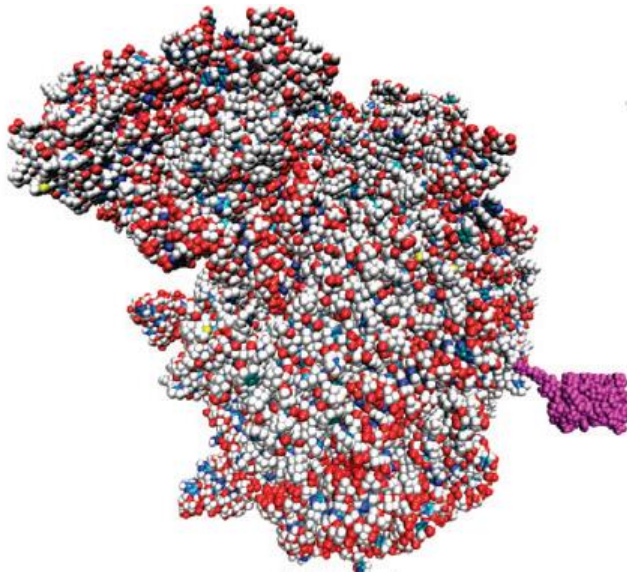
- Combine selected sets of particles into larger particles
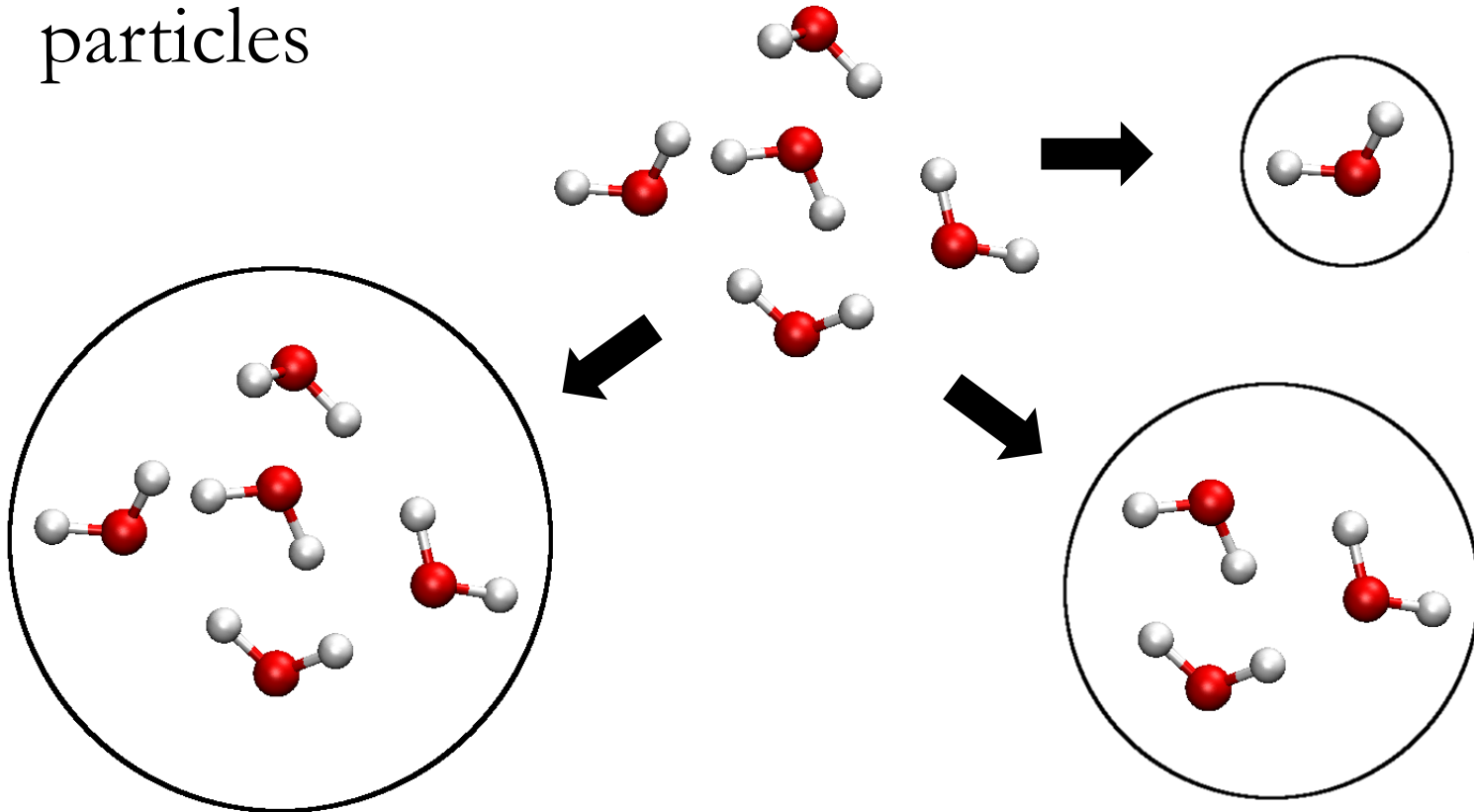
Fine-grained versus coarse-grained models

Loss of accuracy ?

Atomic (fine-grained) level   **Supra-atomic (coarse-grained) level**

Why do coarse-graining?

- Fewer interaction sites → lower computational cost
- Smoother energy surface → longer time step

simulate larger systems for longer timescales

- **But watch out:**
  - only appropriate when details are unimportant
  - loss of entropy
  - modelling "style" depends on purpose:
    - which properties are (inevitably) lost and
    - which properties are to be kept

*Riniker et al., Phys. Chem. Chem. Phys. 14 (**2012**) 12423-12430*
*Riniker & van Gunsteren, J. Chem. Phys. 134 (**2011**) 084110*
*Allison et al., J. Chem. Phys. 136 (**2012**) 054505*

Principles of coarse-graining I

When can particular degrees of freedom be eliminated ?

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Examples: conditions satisfied   conditions *not* satisfied

- CH, CH2, CH3 united atoms   - supra-atomic proteins

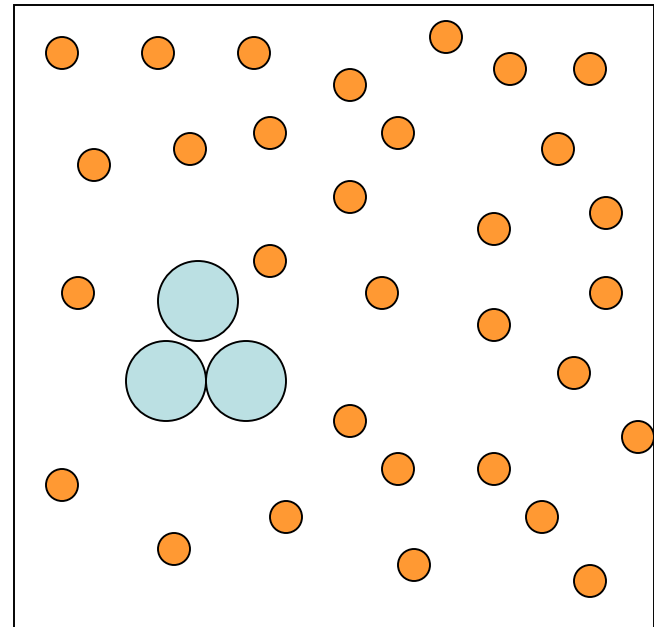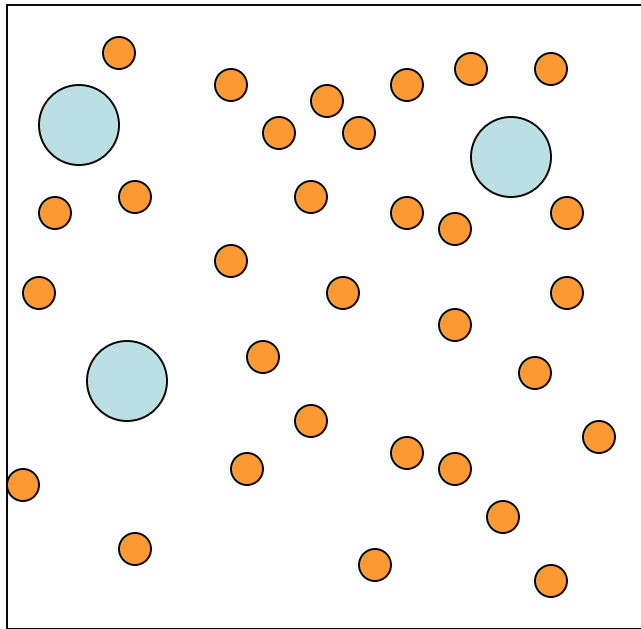- bond-length constraints   - implicit solvent model

The hydrophobic effect

What keeps proteins folded?
Why does oil separate from water?
Why do people who do not know anyone at parties, end up together ?

Particles (*blue ones*) are driven together by favourable interactions
within the environment (*yellow ones*)

This interaction driving the blue particles together
cannot be coarse-grained

Modelling or simulating the hydrophobic effect

Implicit solvent:
- *no aggregation of "hydrophobic" solutes*
- *too strong electrostatic interaction:*
  aggregation of unlike charges
- *no entropy of solvent*
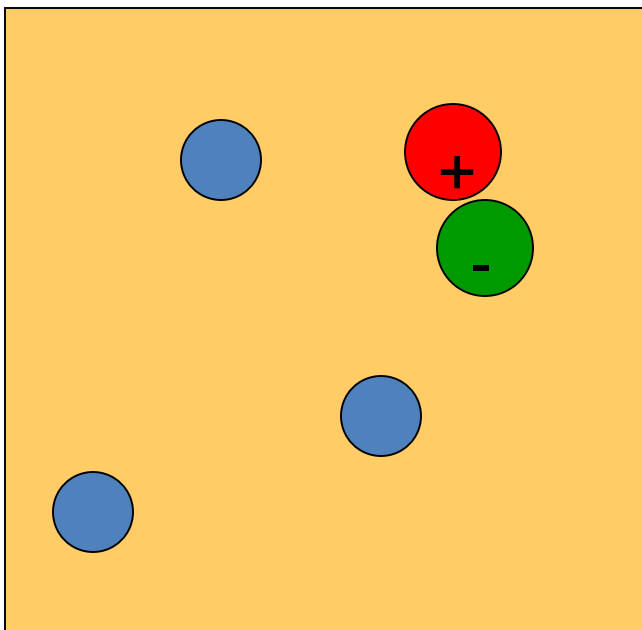
Explicit solvent:
- *aggregation of "hydrophobic" solutes*
- *damped electrostatic interaction:*
  solvation of charges
- *entropy of solvent*
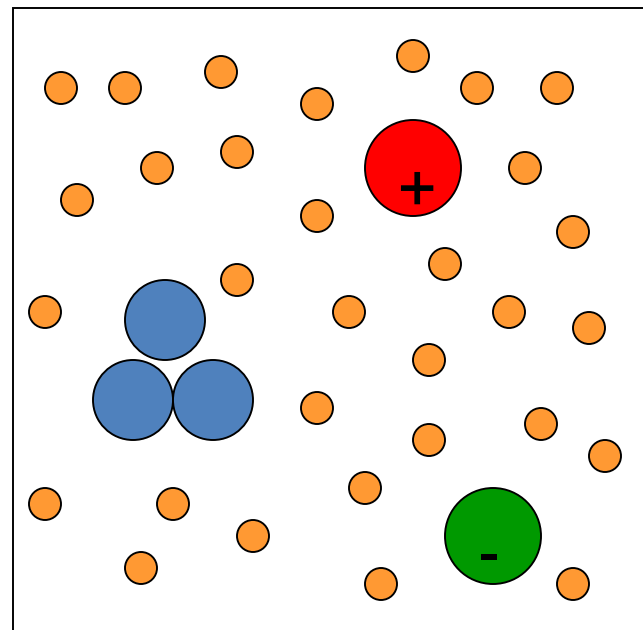
It is *NOT* true that hydrophobic particles do not like water,
rather the interaction of water with water is stronger.
Ions with unlike charges like water more than themselves.

Implicit solvation models are missing the fundamental biomolecular interactions, which are automatically included in explicit solvent simulations

Principles of coarse-graining II

What properties or processes should be maintained (important) ?

1.Molecular structure of the solute (e.g. protein) and structure of the solvent

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4.Dynamic properties: diffusion, viscosity, relaxation times, are less important because most biomolecular processes are thermodynamically driven

Different levels of resolution in modelling

Coarse-graining from a finer-grained level to a coarser-grained level of resolution

Quantum (statistical) mechanics ⟶ Classical (statistical) mechanics

Level of resolution	I	II	III	IV	V
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Coarse-graining only pays off for: level II to level III (not for solvent)
level III to level IV (only for CH_n united atoms)
level III to level V (only for solvent)

Development of a (FG or CG) model I

1. Choice of (FG or CG) degrees of freedom:

   How many FG particles in one CG particle ? Solvent: 2 – 5

   How many interaction sites per (FG or CG) particle ? Solvent: at least 2

2. Choice of functional form of the (FG or CG) interaction:

   van der Waals interaction: r^{-6} attraction

   Fermi-exclusion repulsion: r^{-12} or exponential repulsion

   Coulomb interaction: r^{1} plus reaction field

$$E_{pot} = \sum_{i=1}\sum_{j=1}(\frac{C_{12}}{r_{ij}^{12}} - \frac{C_6}{r_{ij}^6}) + \frac{q_i q_j}{4\pi\varepsilon_0 \varepsilon_{cs}}(\frac{1}{r_{ij}} - \frac{C_{RF} r_{ij}^2}{2R_{RF}^3} - \frac{1 - \frac{1}{2}C_{RF}}{R_{RF}})$$

   Dielectric permittivity in the cut-off sphere ε_{cs} depends on grain level
   $$\varepsilon_{cs}(FG) < \varepsilon_{cs}(CG)$$

   van der Waals parameters C_{12} and C_6 depend on grain level

   in multi-resolution models additional parameters are present:

   permittivity $\varepsilon_{cs}(FG\text{-}CG)$ and $C_{12}(FG\text{-}CG)$ and $C_6(FG\text{-}CG)$

Development of a (FG or CG) model II

3. **_Calibration_** of model parameters: **_only for small molecules_**

       1. Against experimental _thermodynamic data_ for the compounds of

          interest (density, surface tension, heat of vaporisation, excess free energy)

       2. Against _dielectric properties_ of the compounds

       3. Against structural data of the compounds

  I. For single-resolution level models:

      a. single compounds: water, methanol, DMSO, chloroform

      b. mixtures of compounds: water + methanol, + DMSO

  II. For multi-resolution level models:

      a. FG + CG system of single compounds: FG water in CG water

      b. FG + CG system of mixtures of compounds: FG protein in CG water

4. **_Testing_** of (FG or CG) models: **_mainly for large molecules_**

       1. structural data   e.g. protein structure

       2. energetic data   e.g. stability, relative energy of protein structure

       3. dynamic data   e.g. (un)folding time of a polypeptide

Multi-resolution simulation in biochemistry

1. Development of a supra-molecular model for biomolecular or organic solvents:

    a. Pure compounds: H_2O, MeOH, DMSO, $CHCl_3$

    b. Mixtures of these compounds

2. Development of a multi-resolution model for biomolecular systems:

    a. Pure compounds: H_2O, MeOH

    b. Testing for proteins in water: HEWL, CspA, protein G, chorismate mutase (CM)

        1. structure (hydrogen bonding)

        2. stability (energetics)

    c. Testing for peptides in methanol: three beta-peptides

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    a. Lipid tails: n-alkanes

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*Riniker et al. Phys. Chem. Chem. Phys. 14 (**2012**) 12423-12430*
*Meier et al., Angew. Chem. Intl. Ed. 52 (**2013**) 2-17*

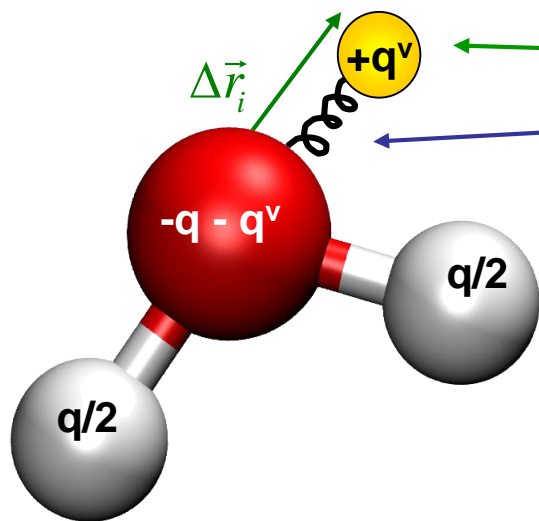# An example of a *sub-atomic* water model: The COS/D2 polarisable model

- ## 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 $\vec{\mu}_i = q_i^v \Delta \vec{r}_i$ $\Delta \vec{r}_i = \vec{r}_i^{\,v} - \vec{r}_O$

**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*

An example of an *atomic* water model: The Simple Point Charge (SPC) model

- ## Three-site FG model:

  - encompasses 1 H_2O molecule, 3 atoms

  - 1 hard-core L-J interaction site, 3 charged sites

  - explicit treatment of electrostatics

  - rigid geometry → no intra-molecular polarisability

0.41e   0.41e

$H^{\delta+}$ $H^{\delta+}$

109.47°

0.1nm   0.1nm

$O^{2\delta-}$

-0.82e

SPC model
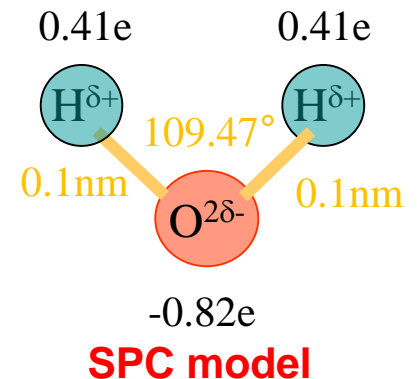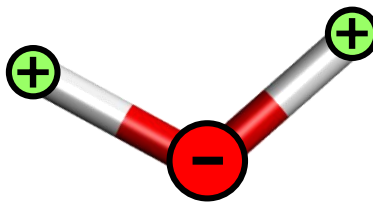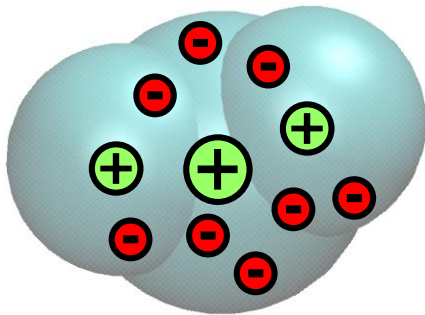
*Berendsen et al., in "Intermolecular Forces", B. Pullman ed., Reidel, Dordrecht (**1981**) 331-342*

An example of a *supra-molecular* (CG) water model

- ## Two-site CG model:

  - encompasses $5\ H_2O$ molecules
  - 1 hard-core L-J interaction site, 2 oppositely charged sites
  - explicit treatment of electrostatics
  - variation of length and orientation of "bond" connecting charged particles → polarisability

m_{DP}, $+q$

r_0, k_b

m_{CW}, $-q$, C_{12}, C_6

=
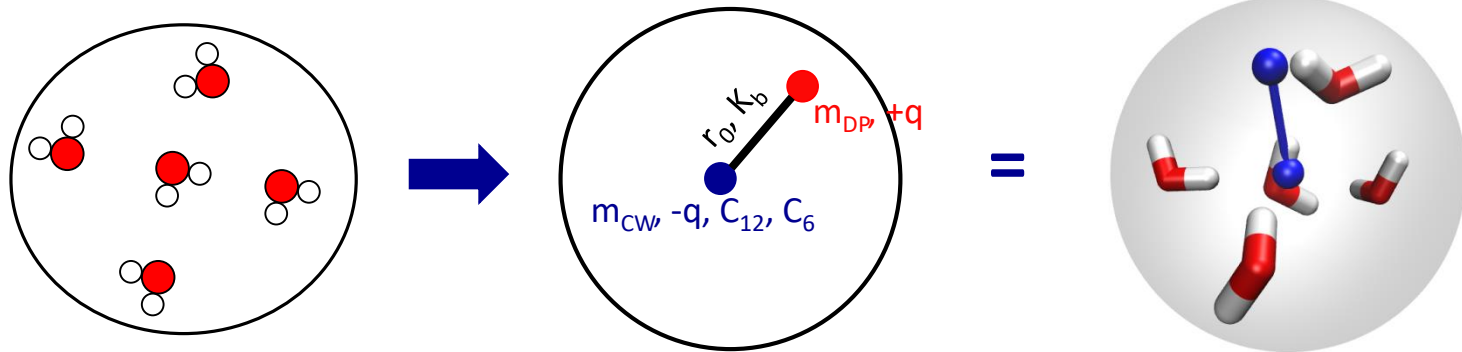
*Riniker & van Gunsteren, J. Chem. Phys. 134 (**2011**) 084110*

Properties of liquid water at different levels of resolution

Properties	Experiment	Sub-atomic level model (COS/D2, 1 H_2O) 2014, 4 sites	Atomic level model (SPC, FG, 1 H_2O) 1981, 3 sites	Supra-molecular level model (CG, 5 H_2O) 2011, 2 sites
ρ (kgm^{-3}) density	997	999	972	995
$\varepsilon(0)$ dielectric permittivity	78.4	78.9	66.6	73.7
γ (10^{-3} Nm^{-1}) surface tension	71.6	63.6	53.4	51.2
C_p (Jmol^{-1}K^{-1}) heat capacity	75.3	88.9	68.9	83.2
α_p (10^{-4} K^{-1}) thermal expansion	4.2	4.9	9.0	26.0
κ_T (10^{-5} atm^{-1}) Compressibility	4.6	4.4	4.7	11.1
D (10^{-9} m^{2}s^{-1}) Diffusion	2.3	2.2	4.2	6.9

☐ **parametrised against**   **Overall "best" model** γ, α_p, D **are off** α_p, κ_T, D **too large**

Trade-off between levels of resolution

The process of coarse-graining may reduce the usefulness of the model in different ways:

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Energy-entropy compensation in liquids

Atomic-level, fine-grained (FG), (non-)polarisable models
Supra-molecular, coarse-grained (CG), polarisable models

		Free energy	*Energy*	$T\Delta S_{vap}$ *Entropy*	$\dfrac{T\Delta S_{vap}}{\Delta H_{vap}}$
	Name of model	ΔF_{exc} $kJ\ mol^{-1}$	ΔH_{vap} $kJ\ mol^{-1}$	ΔH_{vap}-ΔF_{exc} $kJ\ mol^{-1}$	
Water					
experiment		24.0	44.0	20.0	0.45
polarisable FG model	COS/G2	21.8	43.7	21.9	0.50
non-polarisable FG model	SPC	23.6	43.9	20.3	0.46
polarisable CG model	CGW	11.0	25.9	14.9	0.58
Methanol					
experiment		17.8	38.1	20.3	0.53
polarisable FG model	COS/M	14.7	37.8	23.1	0.61
non-polarisable FG model		16.7	37.9	21.2	0.56
polarisable CG model	CGM	7.3	18.0	10.7	0.59

Energy – entropy compensation: $T\Delta S_{vap} \approx \frac{1}{2}\ \Delta H_{vap}$

The CG water has a higher entropy/enthalpy ratio than the FG water
and experiment

Trade-off between levels of resolution

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4. The physical basis of a particular property or process may be changed, leading to an unphysical mechanism of the process in the coarse-grained model

5. The reduction of entropy and energy in the system may lead to an unphysical balance between these two quantities in the coarse-grained model
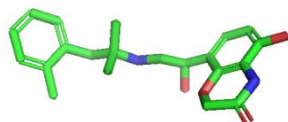
Conclusion:

The combined loss of usefulness on these five counts must be made up for by a much increased computational efficiency of the coarse-grained model

Challenge : **Development of more accurate energy functions (force fields) for biomolecular simulation, at any level of resolution**
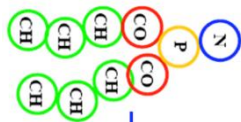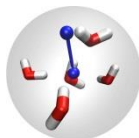
Combining Different Levels of Resolution
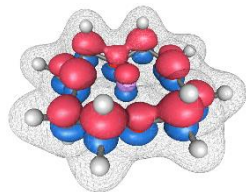
QM description
Nuclei + electrons

QM/MM simulations

Atomistic description
Atoms = point charges

Supra-atomic CG description
Multiple atoms = CG bead

Hybrid atomistic/coarse-grained simulations

Supra-molecular CG description
Multiple molecules = CG bead

Goal:
Reduce computational effort while retaining details for region of interest

Supra-Atomic versus Supra-Molecular

Technical issues

	Supra-atomic	Supra-molecular
CG bead	multiple *atoms*	multiple *molecules*
Pressure correction	no	yes
Cut-off sphere ε_{CS}	1	> 1
Parametrisation method	• Force matching • Iterative Boltzmann • Reverse Monte Carlo	• Fitting to thermodynamic properties (e.g. dielectric permittivity, density, surface tension)
Validation	• Molecular properties (e.g. RDF, free energies, diffusion) • System properties	• Other system properties
Examples	• United atoms (CH_x) • 1:1-water models • Most CG protein, lipid and ligand models	• Solvent models with higher mappings • Ultra coarse-graining (e.g. lipid patches, polymers)

Multi-graining or multi-resolution simulation

Combine different levels of resolution in one system:

1. Switching between levels of resolution for all particles of the system in time: multi-graining in time

   a. Coarse-grained (CG) simulation => map particular configurations to the fine-grained (FG) level

   b. A coupling parameter defines a path between FG and CG representations of particles: smooth switching *(J. Chem. Phys. 124 (2006) 154106)*

2. System contains a mixture of fine-grained and coarse-grained particles: multi-graining in space

   a. Space is divided into fixed FG and CG regions with a buffer region in which particles change character between FG and CG The resolution of particles changes with their position

   b. Particles are either FG or CG and can freely mix *(J. Chem. Phys. 137 (2012) 044120)* The resolution of the particles is fixed

Multi-resolution simulation in biochemistry

1. Development of a supra-molecular model for biomolecular or organic solvents:
   a. Pure compounds: H_2O, MeOH, DMSO, $CHCl_3$
   b. Mixtures of these compounds

2. Development of a multi-resolution model for biomolecular systems:
   a. Pure compounds: H_2O, MeOH
   b. Testing for proteins in water: HEWL, CspA, protein G, chorismate mutase (CM)
      1. structure (hydrogen bonding)
      2. stability (energetics)
   c. Testing for peptides in methanol: three beta-peptides
      3. folding   (structure, energetics, dynamics)

3. Development of a supra-molecular model for lipids:
   a. Lipid tails: n-alkanes

Multi-resolution model for liquid H_2O

Simulation of mixtures of atomic (FG) and supra-molecular (CG) water particles

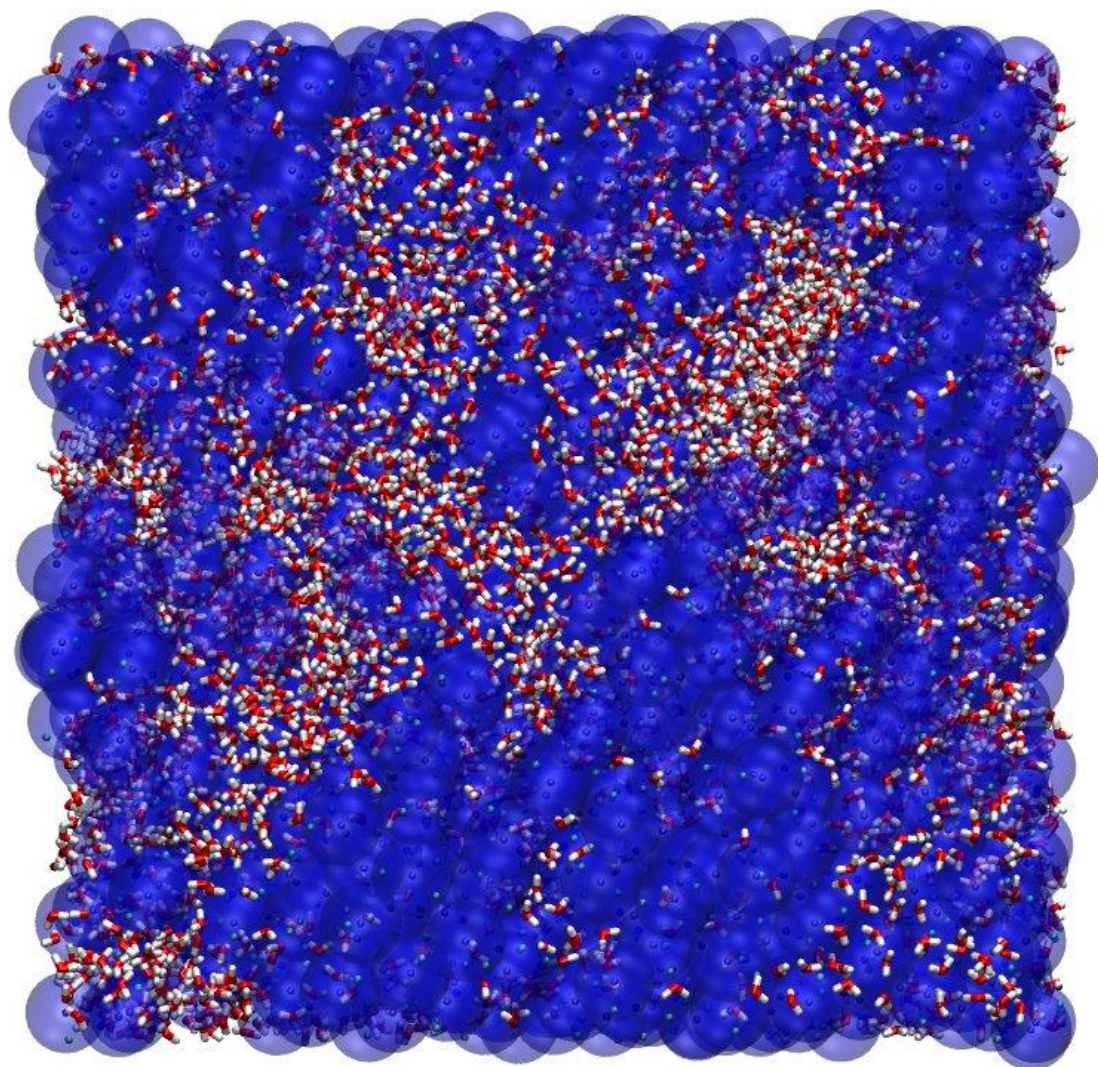Configuration of a 1:1 FG:CG mixture: 6400 FG molecules and 1280 CG beads

One bead
corresponds to
5 H_2O molecules

Relative dielectric
permittivity in the
cut-off sphere:
ε_{cs}(FG-FG) = 1.0
ε_{cs}(FG-CG) = 2.3
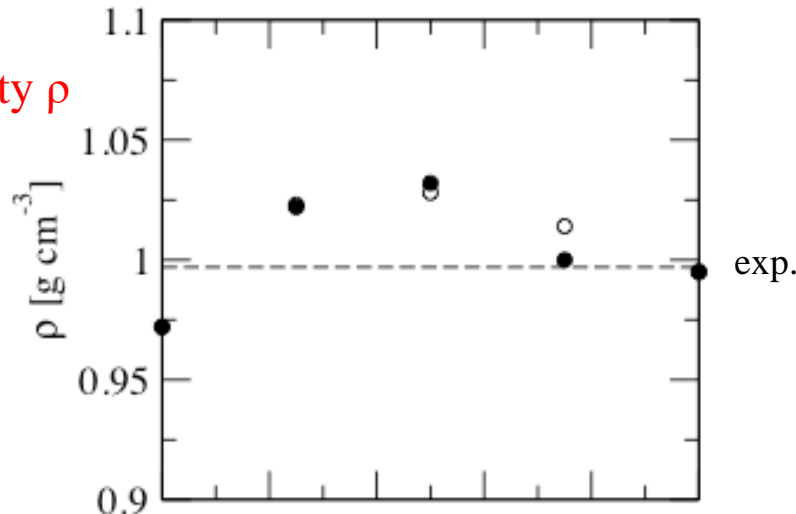ε_{cs}(CG-CG) = 2.5

Riniker & van Gunsteren,
*J. Chem. Phys. 137 (**2012**) 044120*

Multi-resolution model for liquid H₂O

Simulation of mixtures of atomic (FG) and supra-molecular (CG) water particles
Properties as function of *mole fraction x_{CG}* of CG particles (298 K, 1 atm)
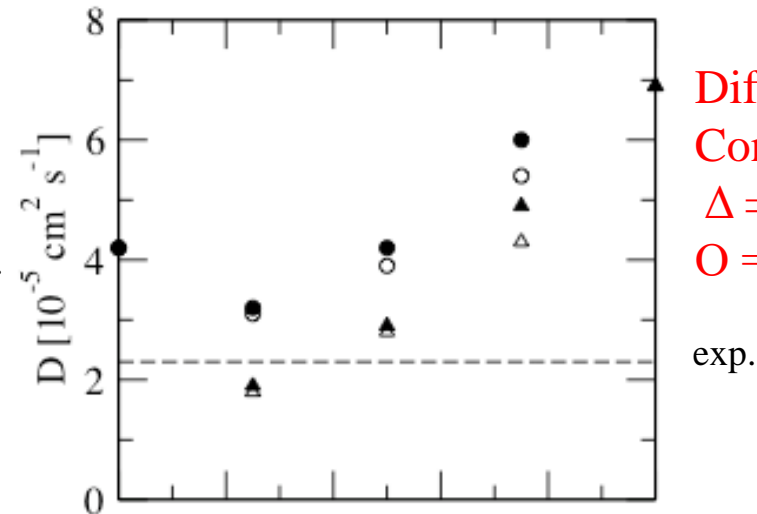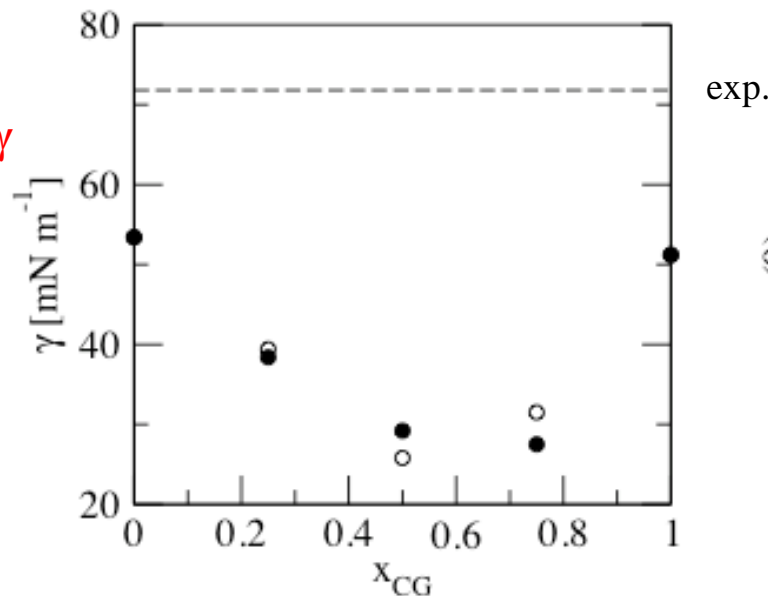

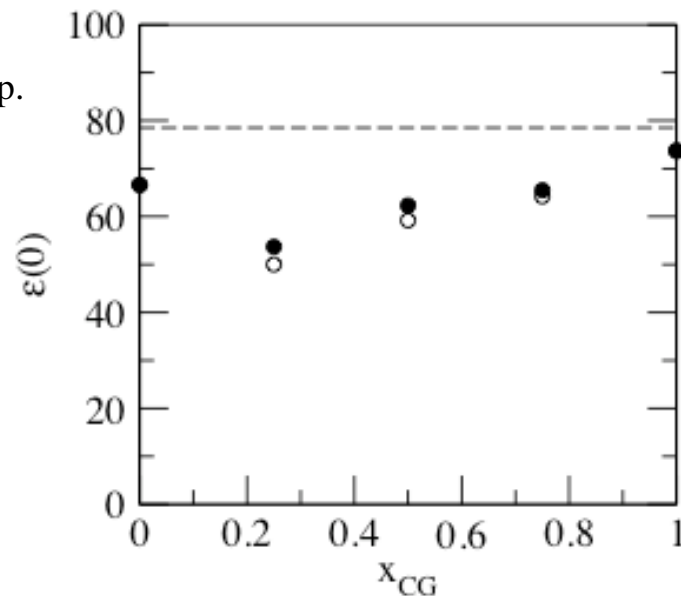Density ρ

Diffusion
Constant D
Δ = CG
O = FG

Surface
tension γ
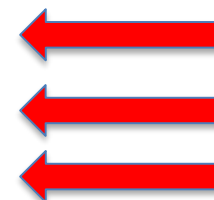
Static
dielectric
permittivity
$\varepsilon(0)$

In an ideal modelling world the properties should not change as function of mole fraction x_{CG}

Multi-resolution model for hydrophobic hydration

Free enthalpy of solvation ΔG_{solv} of an **atomic level (FG) alkane solute**
in *atomic level* **(FG) H_2O** or in *supra-molecular* **(CG) H_2O**

Solute	ΔG_{solv} Exp.[1,2] [kJ/mol]	ΔG_{solv} in FG[3] [kJ/mol]	ΔG_{solv} in CG [kJ/mol]
Methane	8.2	6.2	2.8
Ethane	7.5	7.4	5.3
Propane	8.2	8.6	6.7
Butane	8.8	8.7	8.6
Pentane	9.8	10.2	10.1
Hexane	10.5	11.5	12.2

[1] D. Juchli, *Diploma Thesis at the Laboratory of Physical Chemistry*, ETH Zurich (2000).
[2] S. Cabani, P. Gianni, V. Mollica, L. Lepori, *J. Solut. Chem.*, **10**, 563 (1981).
[3] L. Schuler, X. Daura, W. F. van Gunsteren, *J. Comput. Chem.*, **22**, 1205 (2001).

Multi-graining simulation: the FG-CG interaction is to be calibrated:
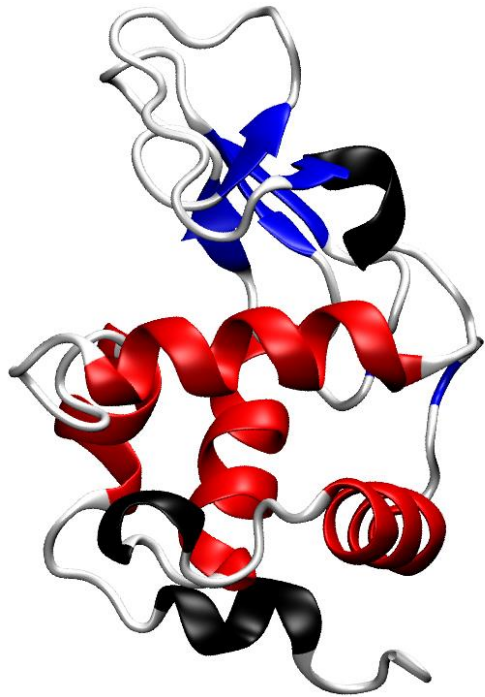- 1. adaption of the van der Waals parameters C_{12}(FG-CG) and C_6(FG-CG)
- 2. adaptation of the dielectric permittivity ε_{cs}(FG-CG) in the cut-off sphere

*Riniker & van Gunsteren, J. Chem. Phys. 137 (**2012**) 044120*

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   c. Testing for peptides in methanol: three beta-peptides
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   a. Lipid tails: n-alkanes

Multi-resolution simulation of four atomic-level (FG) proteins in supra-molecular (CG) water

Hen Egg White Lysozyme (HEWL)
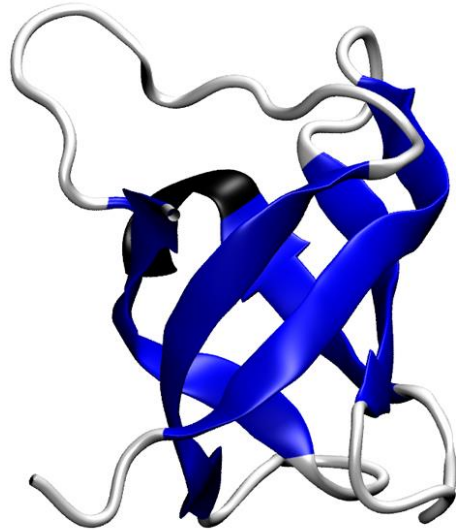
Major cold shock protein (CspA)
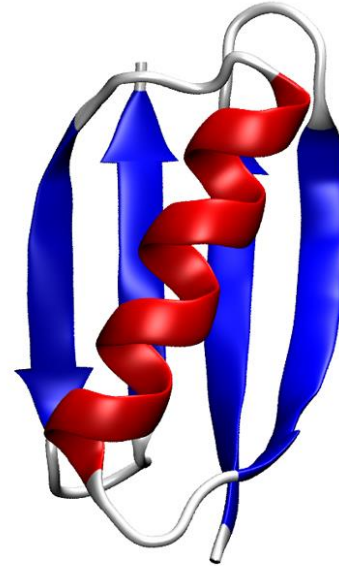
Protein G (PG)
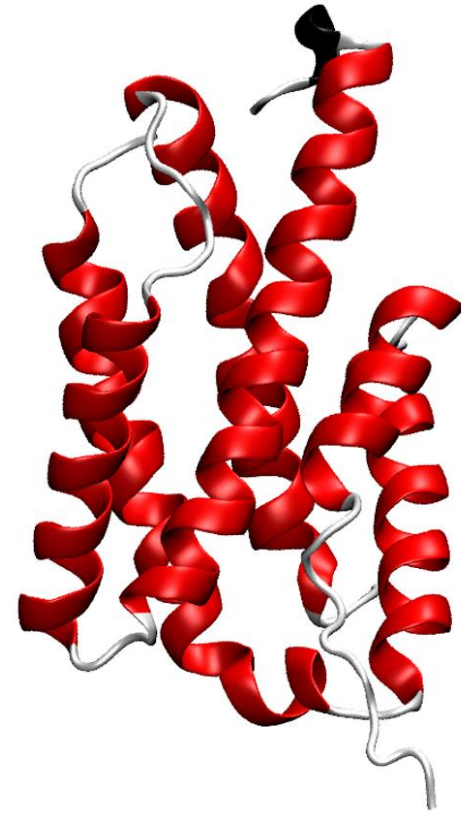
Chorismate mutase (CM)

Multi-resolution simulation of four atomic-level (FG) proteins in supra-molecular (CG) water

Hydrogen bonding:

Left scale (bars):
total number of hydrogen bonds

Right scale (+):
occurrence (%) of hydrogen bonds

Five solvent models:

1. Fully atomic (FG)
2. Atomic layer 0.8 nm
3. Atomic layer 0.4 nm
4. Atomic layer 0.2 nm
5. Fully supra-molecular (CG)
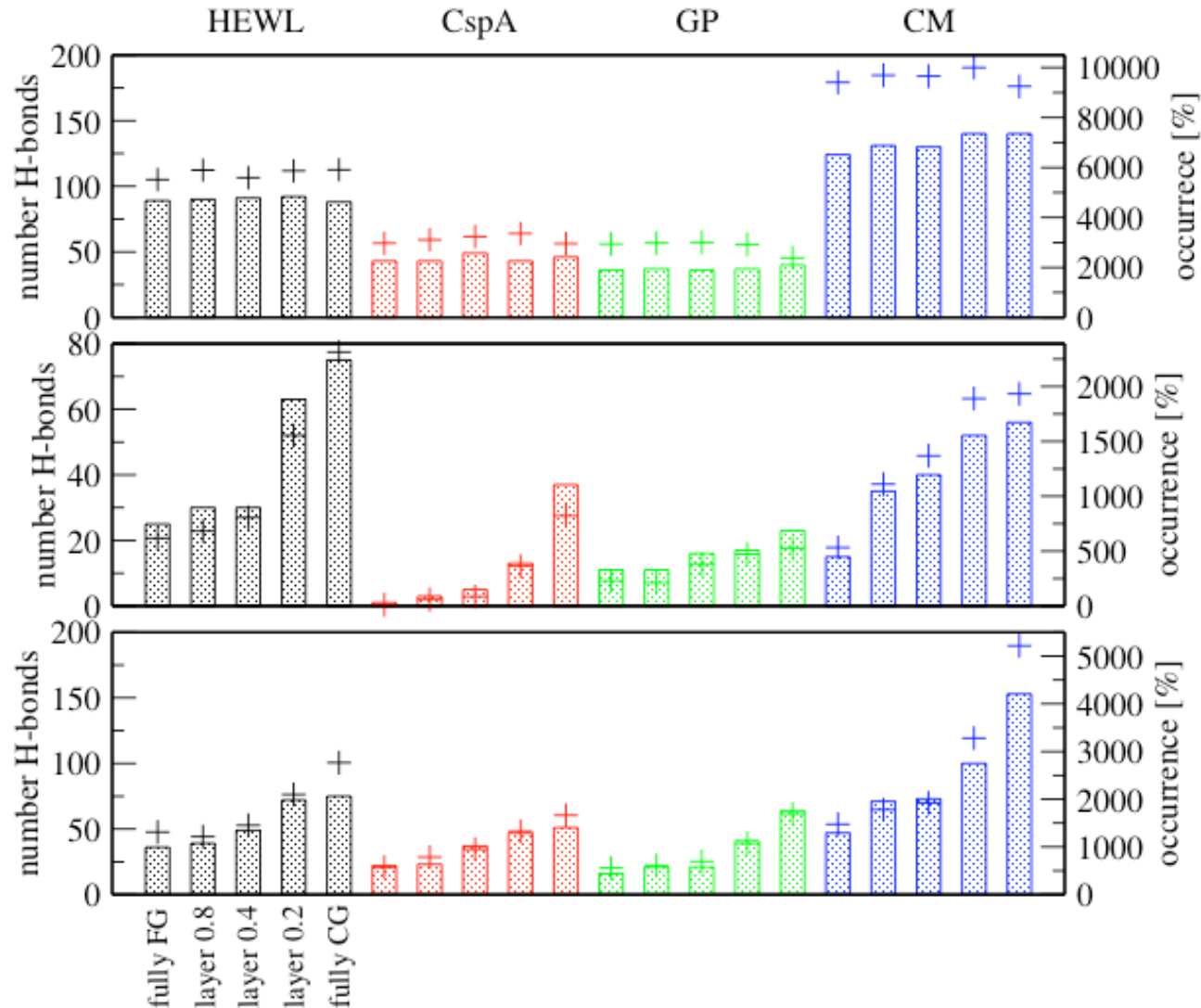
An 0.8 nm atomic (FG) solvent layer around the protein in supra-molecular (FG) water suffices to reproduce the intra-protein hydrogen bonding in a fully (FG) atomic water

Multi-resolution simulation of four atomic-level (FG) proteins in supra-molecular (CG) water

Intra-protein energy:

Total potential energy
V_{pot} *(upper panel)*

Van der Waals energy
V_{LJ} *(middle panel)*

Electrostatic energy
V_{CRF} *(lower panel)*
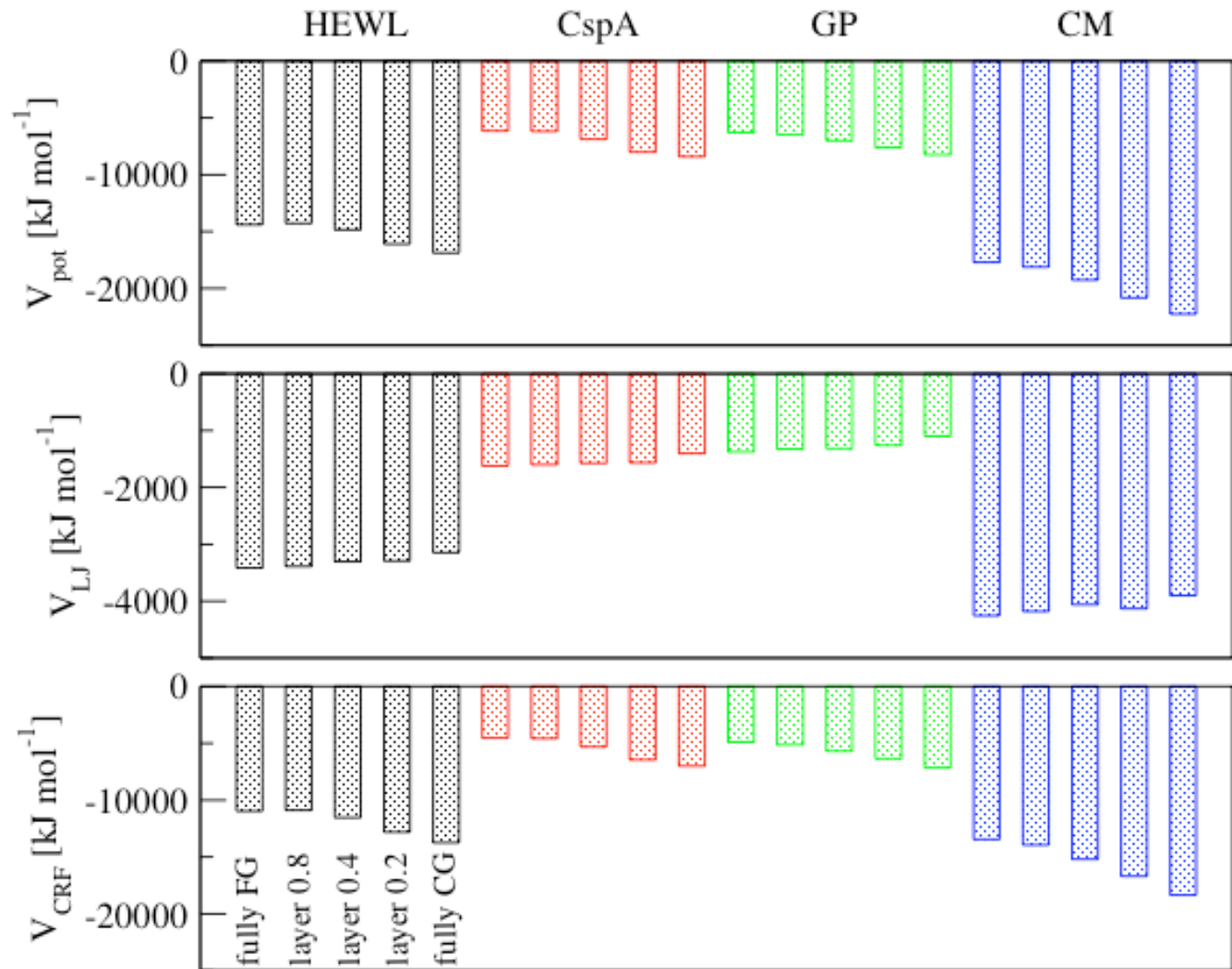
Five solvent models:

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4. Atomic layer 0.2 nm
5. Fully supra-molecular (CG)

An 0.8 nm atomic (FG) solvent layer around the protein in supra-molecular (FG) water suffices to reproduce the intra-protein van der Waals and electrostatic energies in fully (FG) atomic water

Conclusions

Simulation of an atomic-level (FG) protein in supra-molecular (CG) water:
- Secondary structure is stable
- Intra-protein energetics:
    - protein slightly more stable than in fully atomic (FG) water
    - slightly more electrostatic and less van der Waals stabilisation
- Hydrogen bonding:
    - backbone-backbone H-bonding as in fully atomic (FG) water
    - much increased backbone – side-chain and
                    side-chain – side-chain hydrogen bonding
- Simulation is **factor 30 faster** than in fully atomic (FG) water

Simulation of an atomic-level (FG) protein in supra-molecular (CG) water
with a 0.8 nm layer of atomic-level (FG) water around the protein:
- Secondary structure is stable
- Intra-protein energetics as in fully atomic (FG) water
- Hydrogen bonding as in fully atomic (FG) water
- Simulation is **factor 10 faster** than in fully atomic (FG) water

Ala deca-peptide in water:
Differential stability of helices

Influence of solute *force field* and *solvent* model:
SPC = atomic model,   CG = supra-molecular coarse-grained model

GROMOS force field	*Solvent*	$\Delta G_{\pi\alpha} = G_{\pi} - G_{\alpha}$	$\Delta G_{3_{10}\alpha} = G_{3_{10}} - G_{\alpha}$ *(kJ/mol)*
45A3	SPC	5.0±0.5	46.7±1.3
53A6$_{OXY+N}$	SPC	0.8±1.1	38.5±1.0
54A7	SPC	14.3±1.1	36.7±1.2
53A6	*SPC*	5.0±0.8	47.1±2.5
53A6	*CG*	7.6±0.7	37.4±1.5
53A6	*SPC+CG*	4.8±0.7	44.4±1.8

1. Both *solute* and *solvent* model do determine the relative helical stability
2. Force fields 45A3 and 53A6 yield same values
    although having quite different force-field parameters
3. Force field 53A6$_{OXY+N}$ yields too stable π-helix
4. **Supra-molecular (CG) water stabilizes helices having more hydrogen bonds**
5. **Atomic solvent layer (0.8 nm) around solute redresses this effect**

*W. Huang et al., J. Phys. Chem. B 118 (**2014**) 6424-6430*
*Z. Lin et al., J. Chem. Theory & Comput. 9 (**2013**) 1328-1333*

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Development of thermodynamically calibrated fine-grained (FG) and coarse-grained (CG) models for alkane chains

FG
Atomic level model
(no hydrogens)
16 (CH_2 or CH_3) atoms
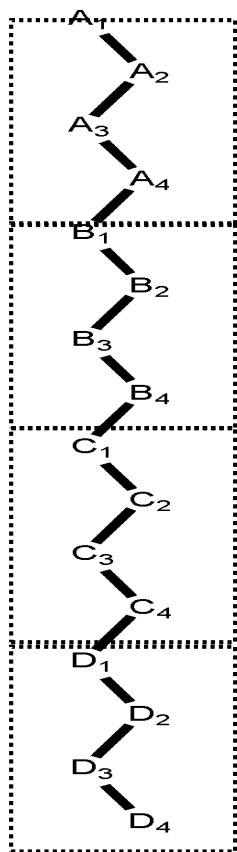
Map 2, 3 or 4 FG united atoms on to one CG particle

CG
Supra-atomic level model
e.g. 1 to 4 mapping
4 particles

Centre of mass
$A_1 - A_4$

Centre of mass
$B_1 - B_4$

Centre of mass
$C_1 - C_4$

Centre of mass
$D_1 - D_4$
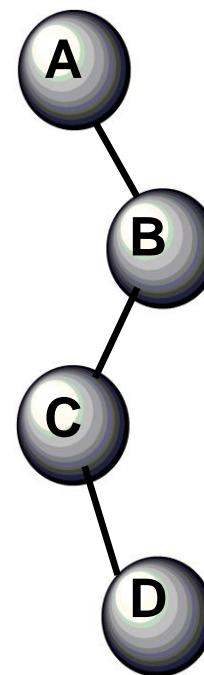
1. Derive **CG** *bonded* interaction parameters from structural characteristics of the mapped *FG configurational ensemble*
2. Calibrate **CG** *non-bonded* interaction parameters against *experimental thermodynamic data* for liquid alkanes

*Eichenberger et al., J. Chem. Theory & Comput. 11 (**2015**) 2925-2937*

Multi-grained simulation of 25 hexadecanes in water

CG + FG   **CG**   **CG**   **CG + FG**

Time: 0 ps   8ps   25ps   100ps

FG   **FG**
8.5ps   25.5ps
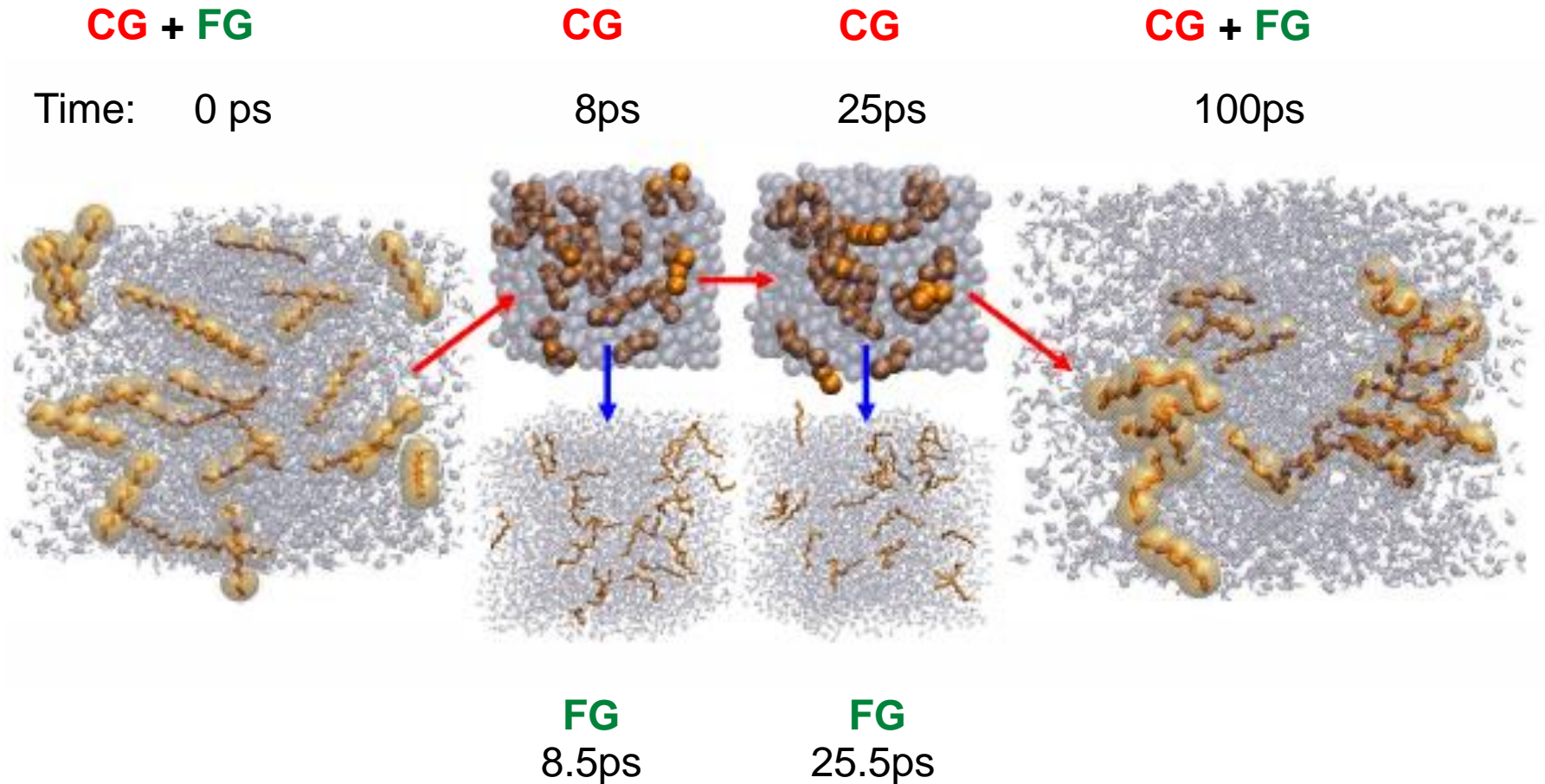
CG level simulation with occasional switching to FG level
enhances exploration of **FG** conformational space
*Interactions at **CG** and **FG** levels should be thermodynamically consistent*

Supra-Atomic CG Alkane Model

Why do alkanes matter ?

Lipid tails

2:1   **3:1**   **4:1**
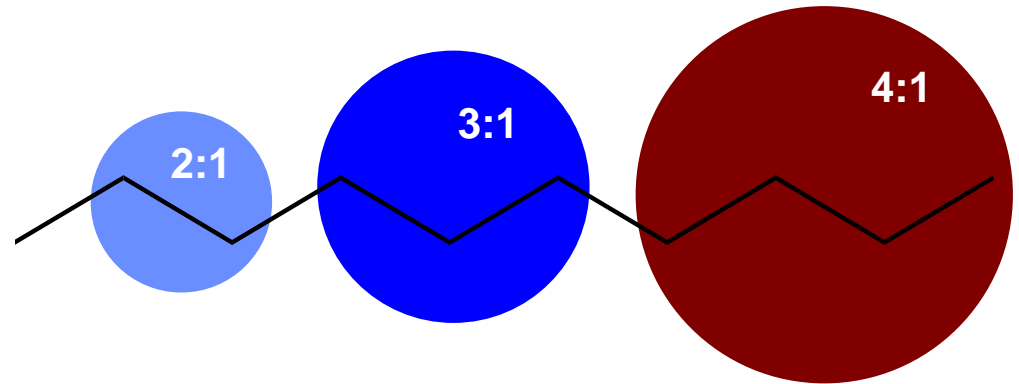
Model:

- Number of CH_2 groups per bead: 2, 3, or 4
- Parameters derived from mapped atomistic simulations
- Fitting to thermodynamic properties
- Different bead types for terminal beads and beads in the middle
- No electrostatic interactions
- LJ parameters averaged over different chain lengths ($C_4 - C_{16}$)
- Unconstrained bonds
- Torsional angle potential energy term present

Derivation of CG bonded interaction parameters from distributions of mapped FG simulated configurations

FG: dashed lines CG: solid lines

FG: red lines CG: black lines

Bond length

Bond angle

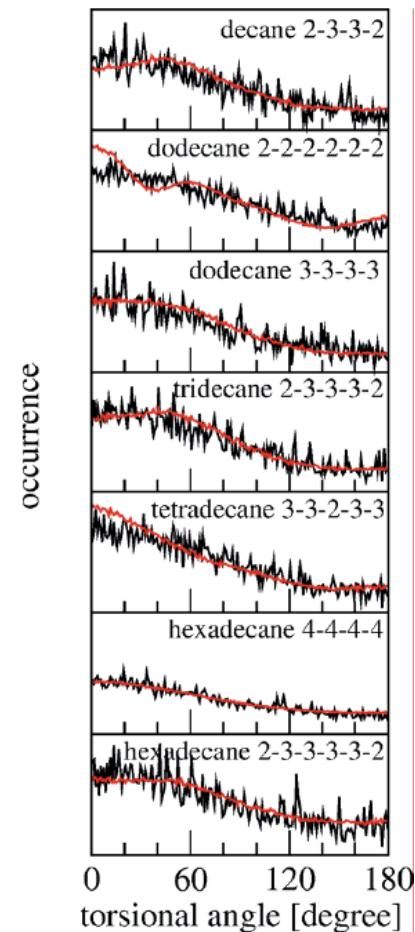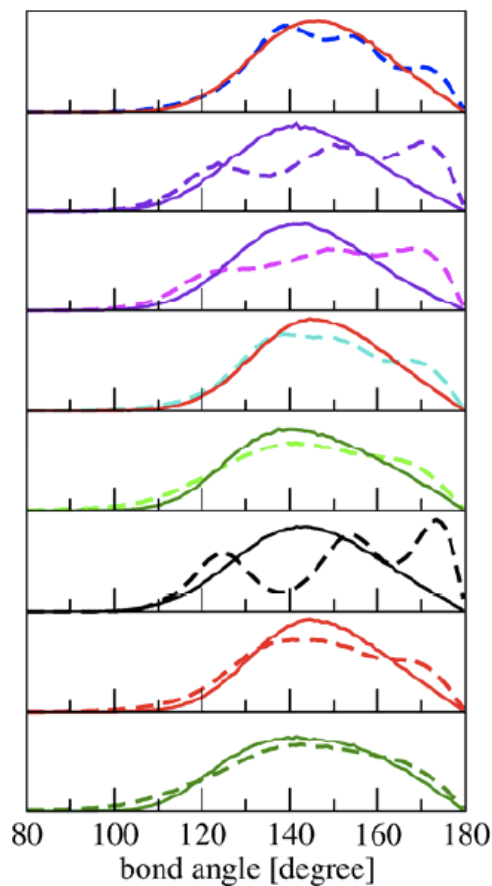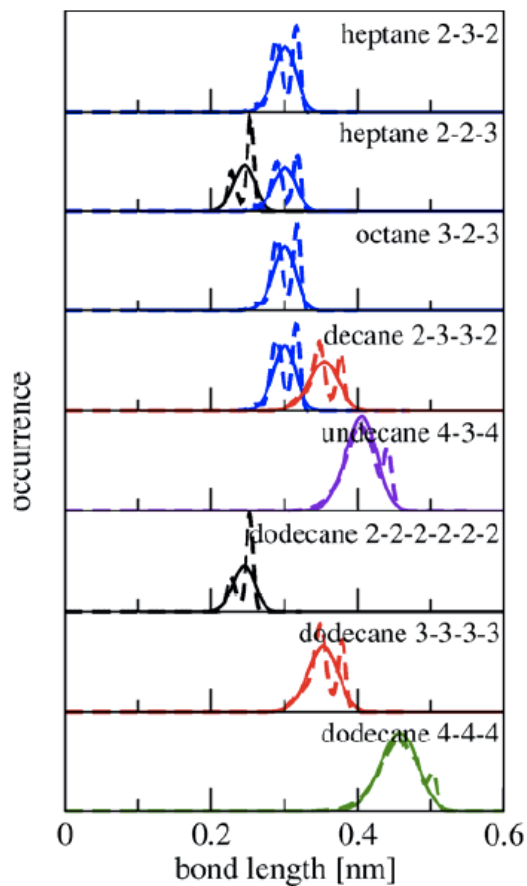**Torsional angle**

Comparison of *FG* simulated and *experimental* thermodynamic data for 18 liquid alkanes: density and heat of vaporisation

Table 1: Number of molecules and atoms in the FG simulations of n-alkanes. Density ρ and heat of vaporisation ΔH_{vap} for liquid alkanes at 298 K and 1 bar, unless indicated otherwise. Experimental values were taken from [43].

alkane	number of		ρ / $\mathrm{kg\,m^{-3}}$		ΔH_{vap} / $\mathrm{kJ\,mol^{-1}}$	
	molecules	atoms	exp.	calc.	exp.	calc.
propane	3334	10002	493.0[a]	495.1	14.79	15.98
butane	2500	10000	573.0[a]	577.8	21.62	21.20
pentane	2000	10000	626.2[b]	621.1	26.43	26.35
hexane	1667	10002	660.6	654.7	31.55	31.71
heptane	1429	10003	679.5	678.7	36.55	36.67
octane	1250	10000	698.6	698.0	41.49	41.38
nonane	1112	10008	719.2[b]	712.6	46.44	46.53
decane	1000	10000	726.6	724.5	51.37	51.56
undecane	910	10010	740.2[b]	734.6	56.33	56.29
dodecane	834	10008	749.5[b]	743.2	61.29	61.53
tridecane	770	10010	756.4[b]	750.4	66.23	66.15
tetradecane	715	10010	759.6[b]	756.4	71.17	71.60
pentadecane	667	10005	768.5[b]	762.0	76.15	76.20
hexadecane	626	10016	770.1	766.8	81.09	81.16
heptadecane	589	10013	778.0[b]	771.4	86.19	86.03
octadecane	556	10008	776.8	774.9	90.79	91.42
nonadecane	527	10013	785.5[b]	778.6	95.81	95.68
eicosane	500	10000	788.6[b]	781.8	100.83	100.87

[a] experimental density measured at a pressure > 1 bar
[b] experimental density measured at a temperature of 293 K

Deviations: density < 1%   heat of vaporisation < 1.2 kJ/mol

Comparison of *CG* simulated and *experimental* thermodynamic data for 14 liquid alkanes: density and heat of vaporisation

alkane	bead sizes	ρ [kg m^{-3}]		ΔH_{vap} [kJ mol^{-1}]	
		exp.	calc.	exp.	calc.
butane	2-2	573.0[a]	572.2	21.62	21.64
pentane	2-3	626.2[b]	623.0	26.43	26.49
hexane	2-2-2	660.6	655.5	31.55	31.87
	3-3		660.0		31.50
heptane	2-3-2	679.5	676.2	36.55	36.87
	2-2-3		683.2		36.72
octane	2-2-2-2	698.6	701.1	41.49	41.40
	4-4		698.0		41.38
	3-2-3		703.0		41.60
nonane	3-3-3	719.2[b]	719.0	46.44	46.45
decane	2-2-2-2-2	726.6	730.0	51.37	51.76
	2-3-3-2		725.5		51.80
undecane	4-3-4	740.2[b]	736.3	56.33	56.26
dodecane	2-2-2-2-2-2	749.5[b]	749.6	61.29	61.08
	3-3-3-3		750.1		61.49
	4-4-4		747.9		61.32
tridecane	2-3-3-3-2	756.4[b]	752.7	66.23	66.67
tetradecane	2-2-2-2-2-2-2	759.6[b]	763.5	71.17	70.85
	3-3-2-3-3		762.1		70.90
pentadecane	3-3-3-3-3	768.5[b]	768.0	76.15	75.82
hexadecane	2-2-2-2-2-2-2-2	770.1	773.3	81.09	80.22
	4-4-4-4		772.5		80.80
	2-3-3-3-3-2		768.5		80.79
heptadecane	3-3-3-2-3-3	778.0[b]	774.5	86.19	84.94

[a] experimental density measured at a pressure > 1 atm
[b] experimental density measured at a temperature of 293 K

Deviations: density < 1%   heat of vaporisation < 1 kJ/mol

Comparison of *CG* simulated and *experimental* thermodynamic data for 14 liquid alkanes:
hydration free enthalpy and excess free energy

alkane	bead sizes	ΔG_{hyd} (kJ mol^{-1})		ΔF_{exc} (kJ mol^{-1})	
		exp.	calc.	exp.	calc.
butane	2-2	8.98	9.09	-	10.09
pentane	2-3	9.74	9.56	14.23	13.27
hexane	2-2-2	10.49	10.80	16.96	16.01
	3-3		10.39		16.48
heptane	2-3-2	11.25	10.53	19.64	19.01
	2-2-3		11.45		19.21
octane	2-2-2-2	12.01	13.47	22.29	22.14
	4-4		11.49		23.27
	3-2-3		12.66		22.31
nonane	3-3-3	12.76	12.58	25.02	25.62
decane	2-2-2-2-2	13.52	15.70	27.74	28.26
	2-3-3-2		13.33		28.32
undecane	4-3-4	14.27	14.58	30.54	32.40
dodecane	2-2-2-2-2-2	15.03	18.55	33.32	34.36
	3-3-3-3		14.79		34.87
	4-4-4		15.31		35.77
tridecane	2-3-3-3-2	15.79	15.60	36.30	37.54
tetradecane	2-2-2-2-2-2-2	16.54	21.37	39.23	40.34
	3-3-2-3-3		17.94		40.72
pentadecane	3-3-3-3-3	17.30	17.83	42.27	44.00
hexadecane	2-2-2-2-2-2-2-2	18.05	24.10	45.51	46.36
	4-4-4-4		18.95		48.15
	2-3-3-3-3-2		18.64		46.54
heptadecane	3-3-3-2-3-3	18.81	19.57	-	49.59

Deviations (excluding *pure* bead sizes 2 and 4): $\Delta G_{hydr} < 1$ kJ/mol $\Delta F_{exc} < 1$ kJ/mol

Comparison of *CG* simulated and *experimental* thermodynamic and dynamic data for 14 liquid alkanes:
surface tension *γ*, viscosity *η* and diffusion *D*

| alkane	bead sizes	γ (mN m^{-1})		η (cp)		D (10^{-5} cm^{2}s^{-1})	
		exp.	calc.	exp.	calc.	exp.	calc.
butane	2-2	12.4[a]	14.4	0.20[b]	0.14	-	7.93
pentane	2-3	15.5	18.3	0.22	0.19	5.16[a]	5.34
hexane	2-2-2	17.9	21.7	0.30	0.23	4.21	4.73
	3-3		25.5		0.25		3.76
heptane	2-3-2	19.7	25.2	0.39	0.26	3.12	3.89
	2-2-3		25.5		0.31		3.49
octane	2-2-2-2	21.1	24.3	0.51	0.25	2.00	3.43
	4-4		31.6		0.43		1.95
	3-2-3		24.9		0.33		2.55
nonane	3-3-3	22.4	24.3	0.66	0.41	1.70	1.99
decane	2-2-2-2-2	23.4	26.2	0.84	0.42	1.31	2.49
	2-3-3-2		29.0		0.34		2.17
undecane	4-3-4	24.2	25.8	1.10	0.50	0.98	1.08
dodecane	2-2-2-2-2-2	25.3[a]	25.8	1.38	0.35	0.81	1.97
	3-3-3-3		32.6		0.48		1.32
	4-4-4		30.4		0.80		0.85
tridecane	2-3-3-3-2	25.6	26.2	1.72	0.43	0.61	1.42
tetradecane	2-2-2-2-2-2-2	26.1	28.8	2.13	0.38	0.52	1.60
	3-3-2-3-3		29.4		0.48		1.08
pentadecane	3-3-3-3-3	27.1[a]	30.8	2.53	0.59	0.40	0.88
hexadecane	2-2-2-2-2-2-2-2	27.0	25.2	3.03	0.37	0.38	1.44
	4-4-4-4		33.0		0.82		0.45
	2-3-3-3-3-2		25.8		0.47		1.04
heptadecane	3-3-3-2-3-3	27.9[a]	32.4	3.29[c]	0.51	0.36	0.83

γ generally bit too large   η too low and D too large

Comparison of *CG* simulated and *experimental* secondary thermodynamic data for 14 liquid alkanes:
heat capacity C_p, thermal expansion a_T and compressibility κ_T

alkane	bead sizes	C_p ($J\,K^{-1}\,mol^{-1}$)		α_T ($10^3\,K^{-1}$)		κ_T ($10^{-5}\,atm^{-1}$)	
		exp.	calc.	exp.	calc.	exp.	calc.
butane	2-2	140.9	105.4	2.1[a]	1.7	–	27.3
pentane	2-3	167.2	116.3	1.6	1.3	21.8	19.1
hexane	2-2-2	195.6	152.6	1.4	1.2	16.7	15.6
	3-3		128.8		1.1		16.5
heptane	2-3-2	224.7	166.8	1.3	1.1	14.4	14.2
	2-2-3		165.3		1.0		15.2
octane	2-2-2-2	254.6	202.6	1.2	1.0	12.8	13.7
	4-4		154.8		0.9		13.0
	3-2-3		178.6		0.9		14.0
nonane	3-3-3	284.4	193.3	1.1	0.9	11.8	12.3
decane	2-2-2-2-2	314.4	253.5	1.0	0.9	10.9	12.2
	2-3-3-2		230.9		0.9		11.5
undecane	4-3-4	344.9	219.7	1.0	0.8	10.3	10.4
dodecane	2-2-2-2-2-2	375.8	304.4	0.9	0.8	9.9	10.6
	3-3-3-3		258.0		0.8		10.8
	4-4-4		233.4		0.8		10.3
tridecane	2-3-3-3-2	406.7	295.2	0.9	0.8	9.5	10.0
tetradecane	2-2-2-2-2-2-2	438.5	354.7	0.9	0.8	9.1	10.6
	3-3-2-3-3		308.2		0.8		10.4
pentadecane	3-3-3-3-3	473.7	322.3	0.9	0.8	8.8	9.9
hexadecane	2-2-2-2-2-2-2-2	501.6	406.6	0.9	0.8	8.6	10.3
	4-4-4-4		313.3		0.7		9.8
	2-3-3-3-3-2		361.5		0.8		9.8
heptadecane	3-3-3-2-3-3	534.7	374.4	0.9	0.8	8.2	9.4

heat capacity C_p too low   **thermal expansion α_T and compressibility κ_T are fine**

Supra-Atomic CG Alkane Model

Comparison with experimental data
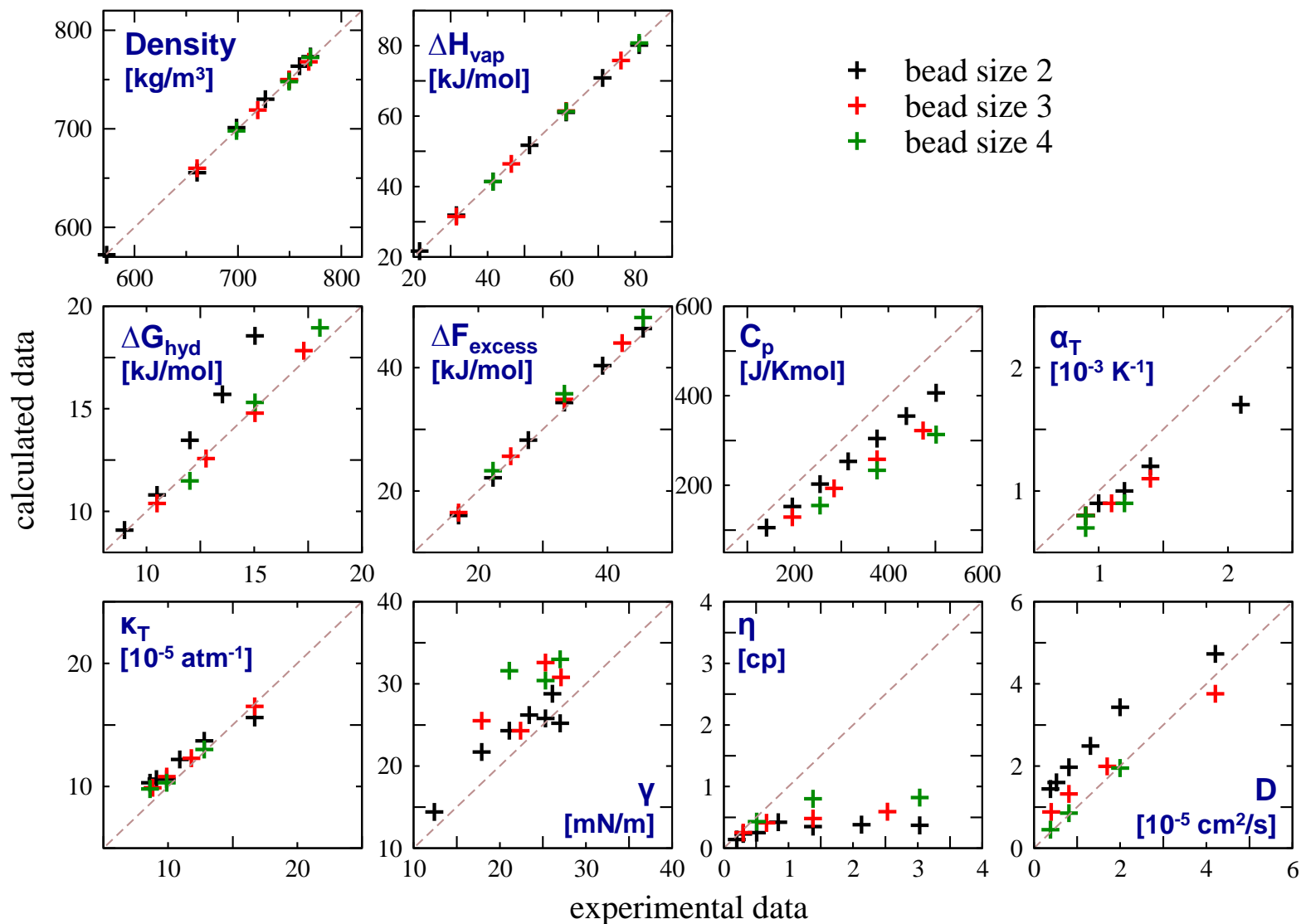
Supra-Atomic CG Alkane Model

2:1-mapping
Well reproduced properties
- RDF
- Surface tension
- Heat capacity

Less well reproduced properties:
- Free energy of hydration
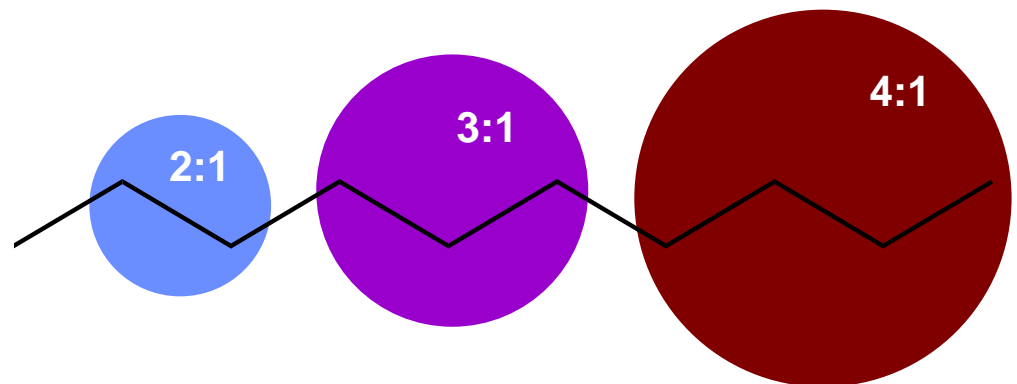- Diffusion coefficient

4:1-mapping
Well reproduced properties
- Free energy of hydration
- Diffusion coefficient

Less well reproduced properties:
- RDF → too structured!
- Surface tension
- Heat capacity

➡ **3:1-mapping is a good compromise**

Multi-resolution simulation in biochemistry

1. Development of a supra-molecular model for biomolecular or organic solvents:
   a. Pure compounds: H_2O, MeOH, DMSO, $CHCl_3$
   b. Mixtures of these compounds

2. Development of a multi-resolution model for biomolecular systems:
   a. Pure compounds: H_2O, MeOH
   b. Testing for proteins in water: HEWL, CspA, protein G, chorismate mutase (CM)
       1. structure (hydrogen bonding)
       2. stability (energetics)
   c. Testing for peptides in methanol: three beta-peptides
       3. folding   (structure, energetics, dynamics)

3. Development of a supra-molecular model for lipids:
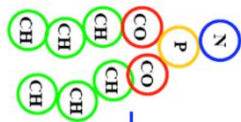   a. Lipid tails: n-alkanes
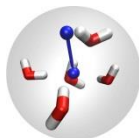
Combining Different Levels of Resolution
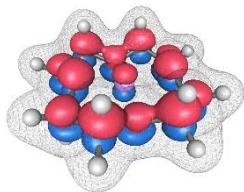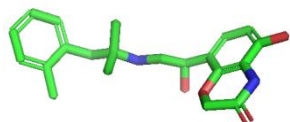
QM description
Nuclei + electrons

QM/MM simulations

Atomistic description
Atoms = point charges

Supra-atomic CG description
Multiple atoms = CG bead

Hybrid atomistic/coarse-grained simulations

Supra-molecular CG description
Multiple molecules = CG bead

➡ **Goal:**
Reduce computational effort while retaining details for region of interest

Coarse-graining

Goal: striking an *appropriate* balance between accuracy and computational cost
while maintaining a *physically correct mechanism* of the process of interest

Coarse-graining (CG) = reduction of degrees of freedom
Sub-atomic (QM) → atomistic → supra-atomic → supra-molecular

**Supra-*atomic* vs. supra-*molecular* CG models**
- Effect on parametrisation strategy
- Effect on properties that can be compared/reproduced (loss of information)
- Supra-molecular models:
    - ➢ Larger loss in entropy to compensated in enthalpy
    - ➢ Faster diffusion due to smoother energy surface
    - ➢ Pressure correction

Combining levels of resolution
- Region of interest needs to include an atomistic solvent layer
- Fixed resolution: How to deal with boundary between atomistic and coarse-grained solvent?

Three-resolution level system simulated (5 nsec)

a. First substrate: nuclei + electrons   (QM, level II)
b. Second substrate: atomic and supra-atomic   (CM, levels III + IV)
c. Protein (dimer)   atomic and supra-atomic   (CM, levels III + IV)
d. Solvent (water)   supra-molecular   (CM, level V)
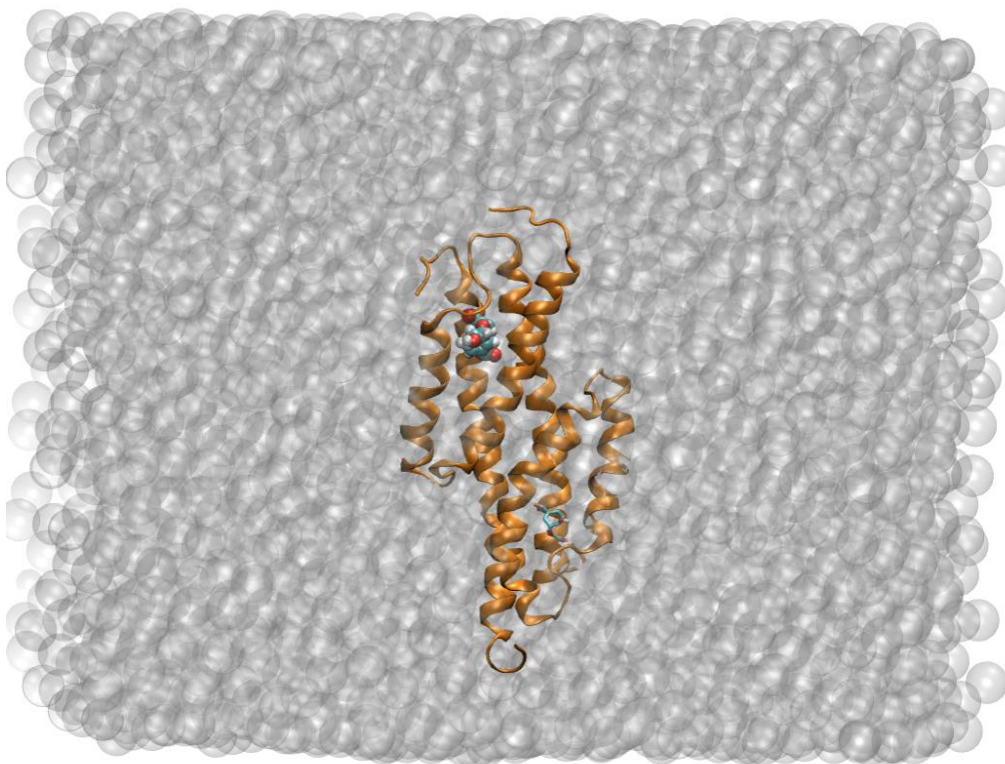
*Meier et al., Angew. Chem. Intl. Ed. 52 (**2012**) 2820-2834*
*Choutko et al., Protein Science 22 (**2013**) 809-822*

Choosing a model for simulating a particular process

I. Determine the ***important grain level(s)*** with respect to the process of interest

II. For each important grain level:

1) Detect the ***essential degrees of freedom*** for the properties of interest by considering experimental data + confounding variables

2) Make corresponding simplifications and approximations:
   simplifications: keep essential interactions (≠ degrees of freedom)

   approximations: keep inaccuracies balanced (overall accuracy determined by worst approximation)

3) Decide which (experimental) data to use for ***calibration***

4) Find other, independent experimental data for ***testing***

not detectable →

not known →

accuracy too low →

not available →

Quit modelling or **produce pretty pictures without physical meaning**

not available →

No test of model possible

III. Use multi-grained or multi-resolution simulation:

1) Switch between different grain levels in time or as function of a coupling parameter λ

2) Combine different grain levels in space, e.g.
   electronic ⟺ atomic
   atomic ⟺ supra-molecular
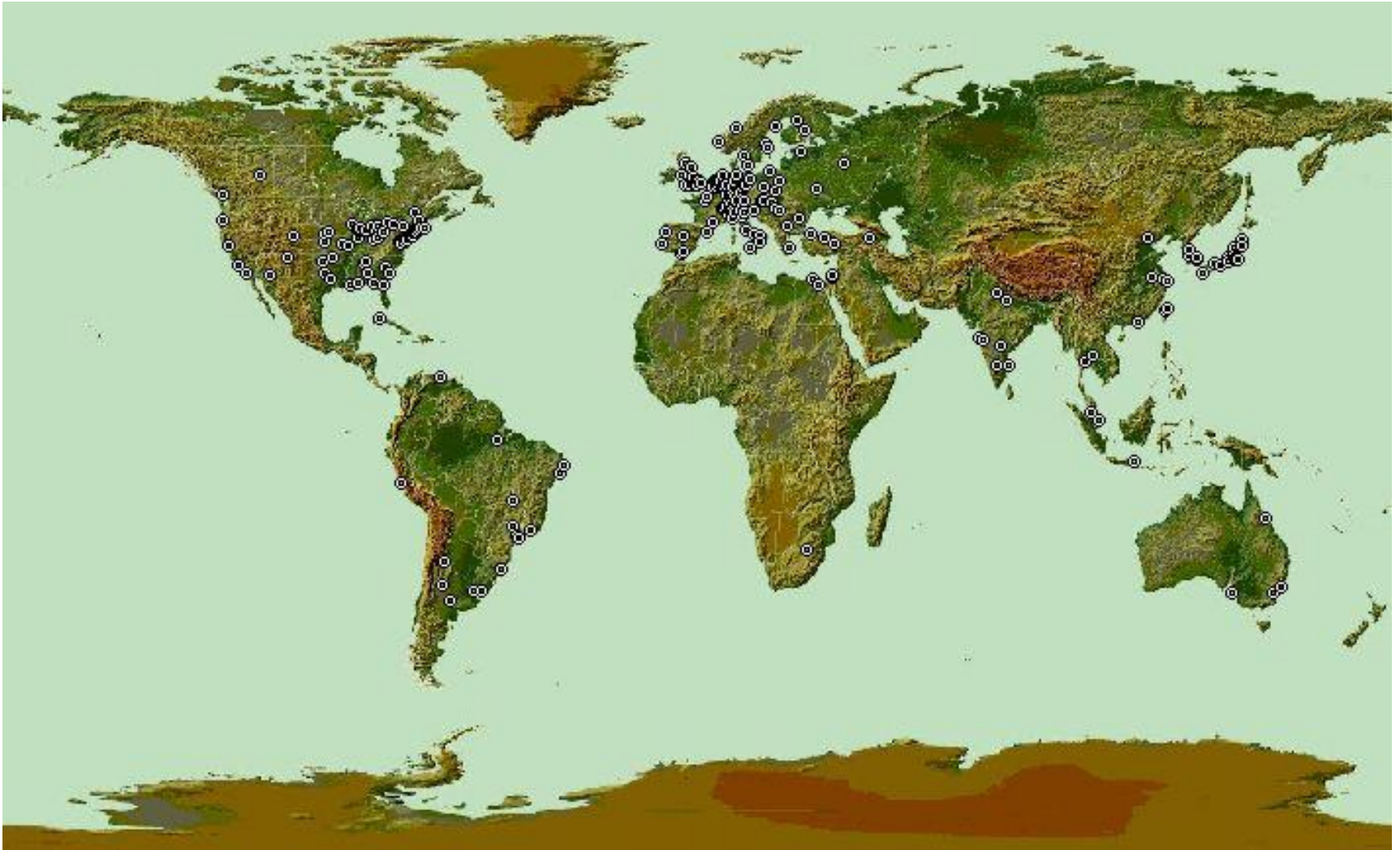
Riniker et al.
Phys. Chem. Chem. Phys. 14
*(**2012**) 12423-12430*

Meier et al.,
Angew. Chem. Intl. Ed.
*52 (**2013**) 2-17*

Different levels must be thermodynamically consistent

Spatial distribution of licences
GROMOS biomolecular simulation software

GROMOS = Groningen Molecular Simulation + GROMOS Force Field

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