Multiscale Modeling

Winterschool on
Theoretical Chemistry and Spectroscopy
10-14 December, 2012

Bernd Ensing
University of Amsterdam

ACMM Amsterdam Center for Multiscale Modeling

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Background

Car-Parrinello MD study of chemical reactions in water

Rare events, free energy methods, sampling methods

Hybrid multiscale MD

Photoactive proteins

Electro-chemistry, redox reactions

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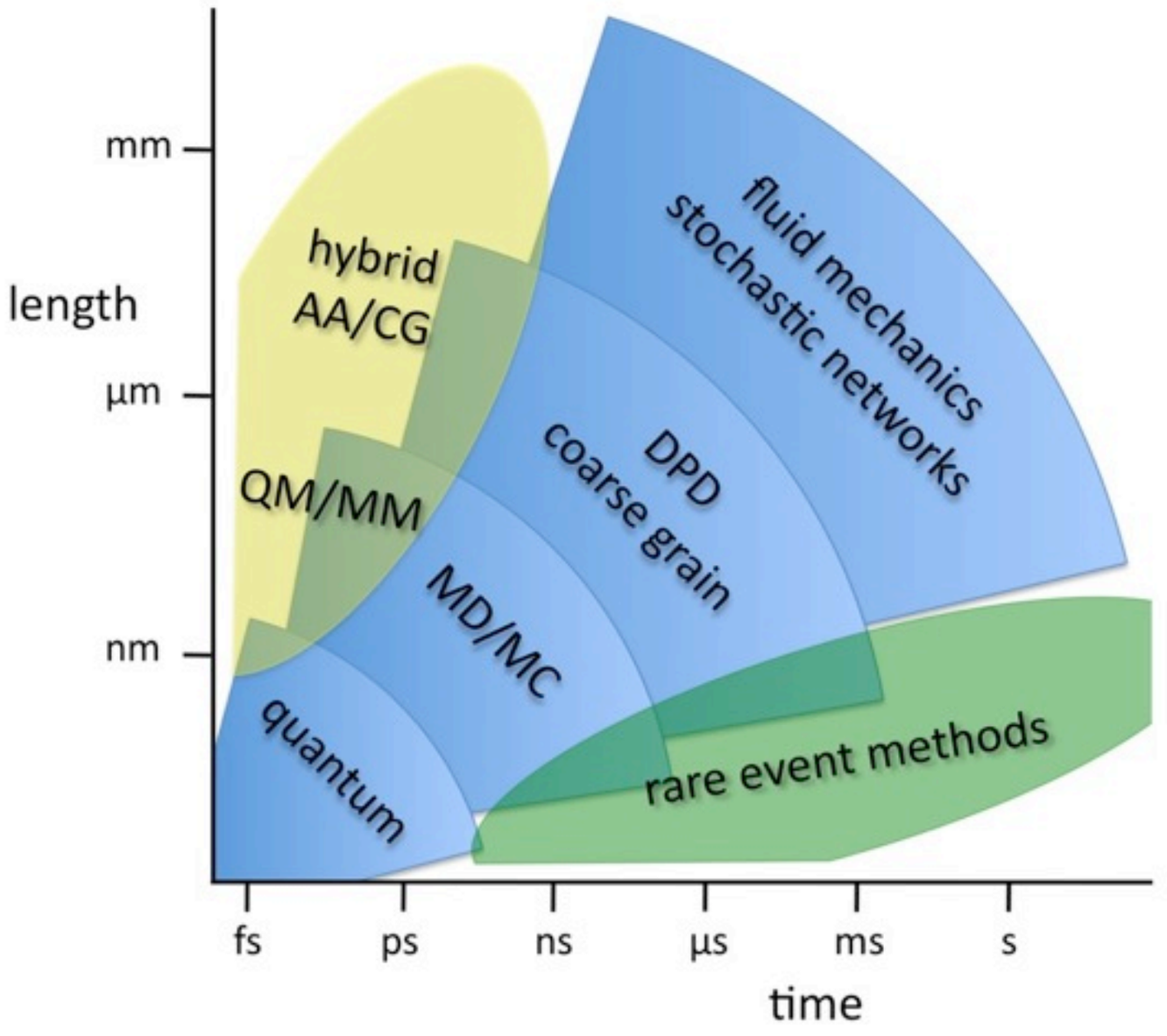
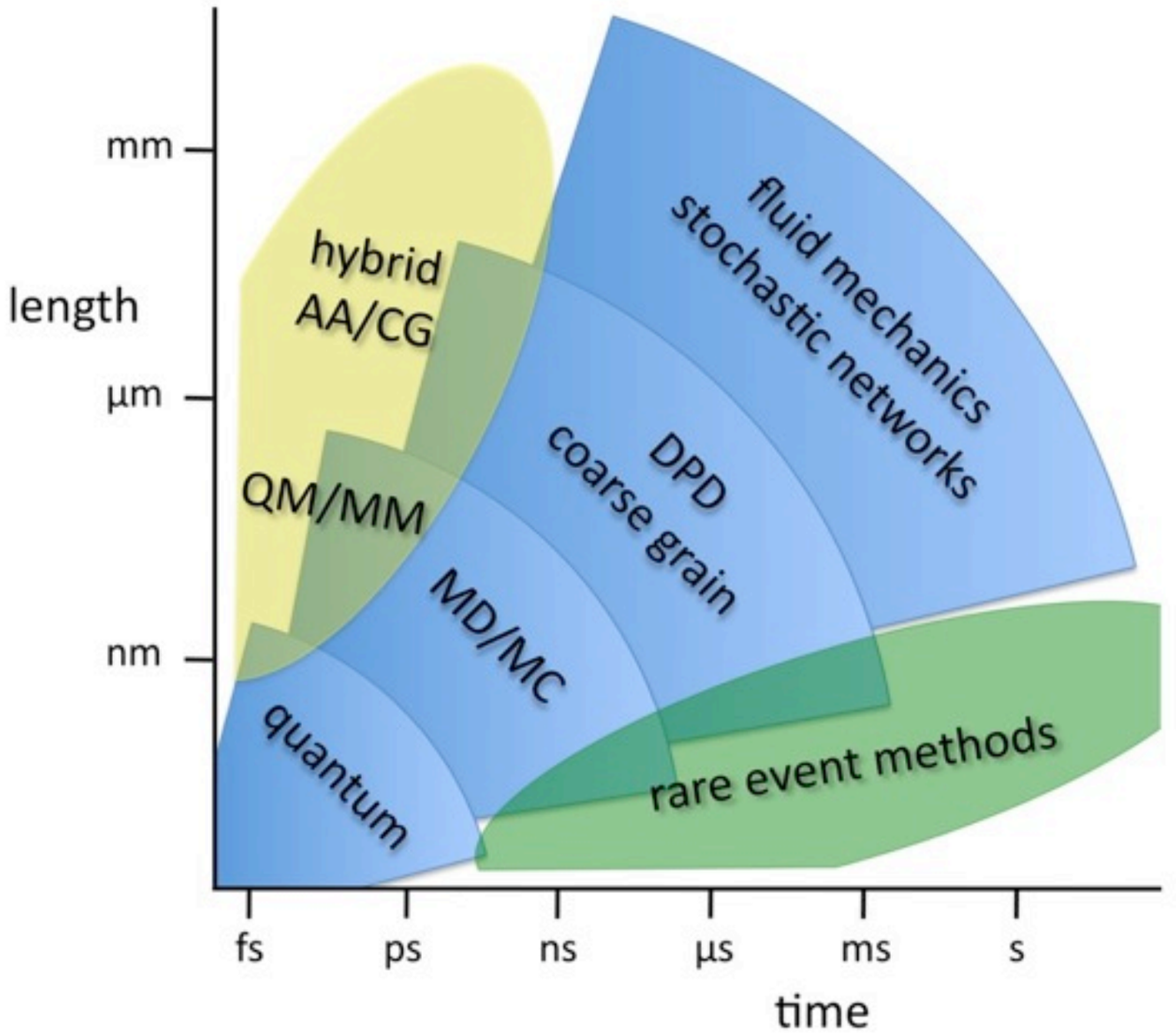
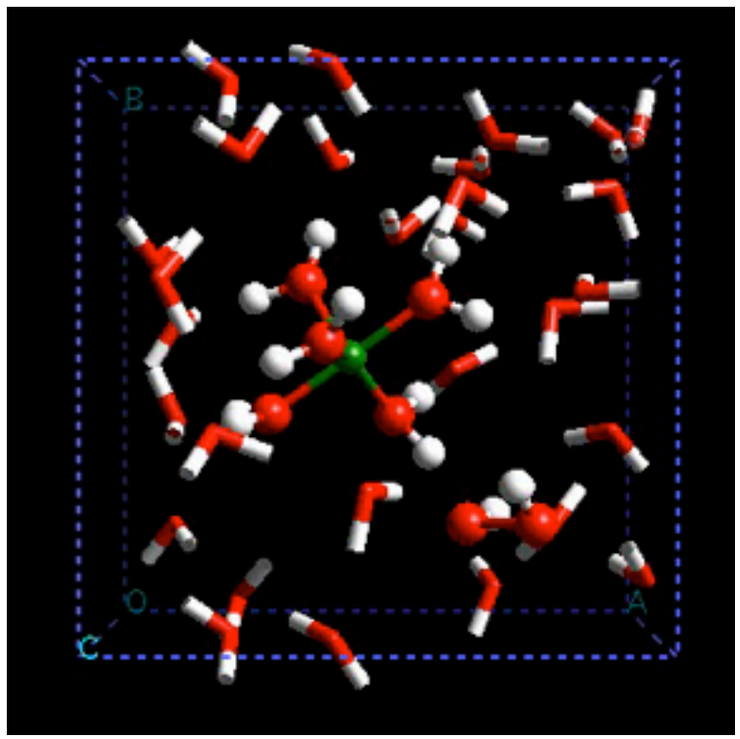
Spatial/Temporal scales in computational modeling



Spatial/Temporal scales in computational modeling



quantum



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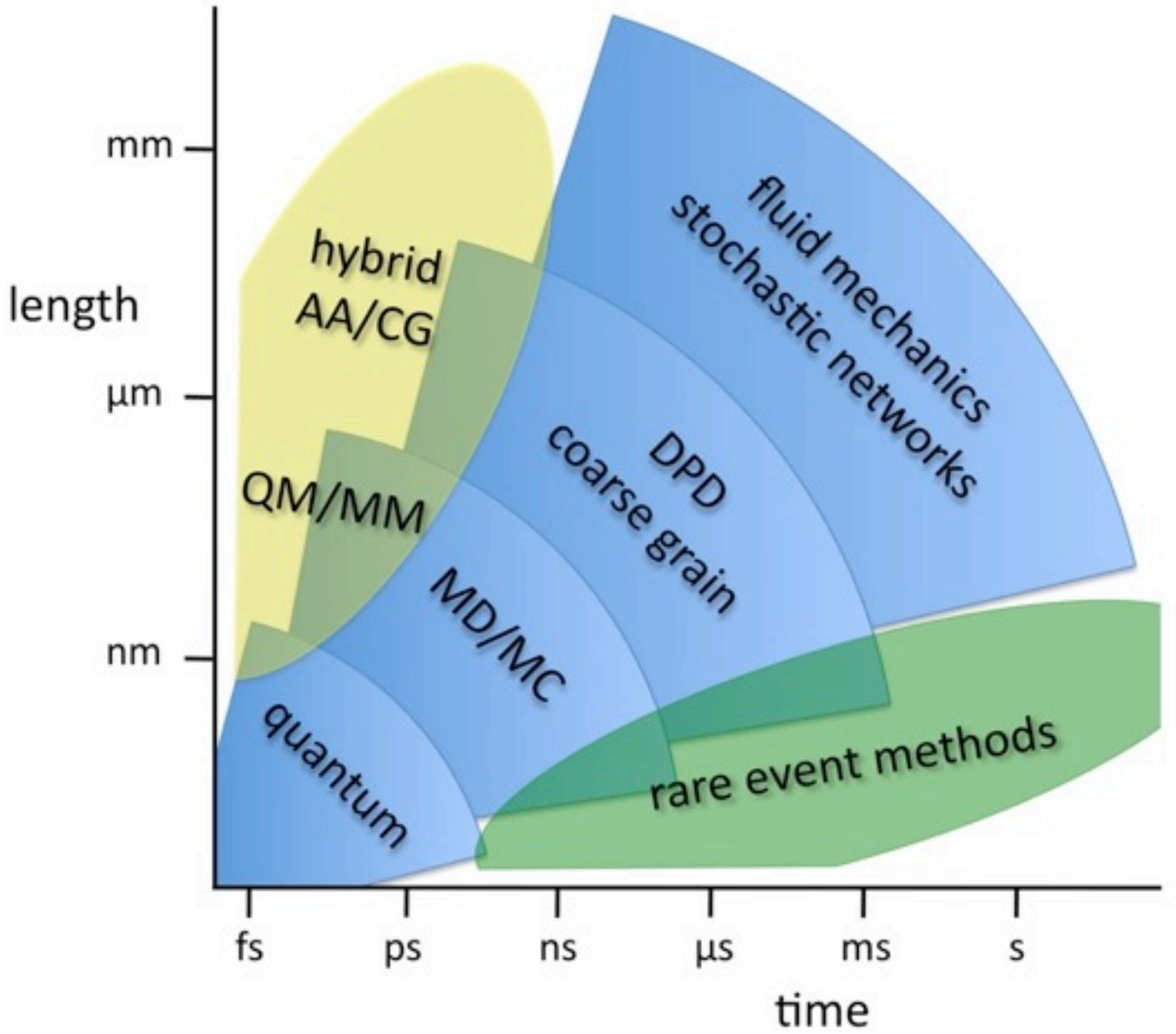
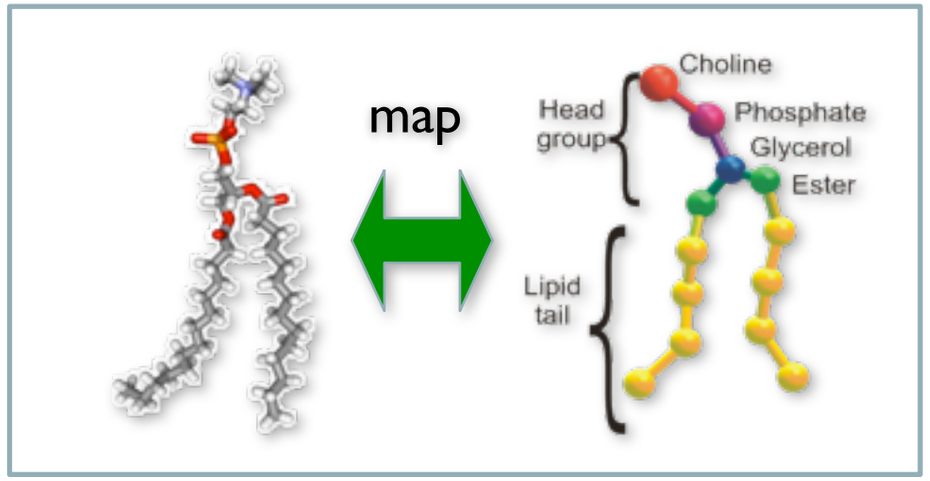
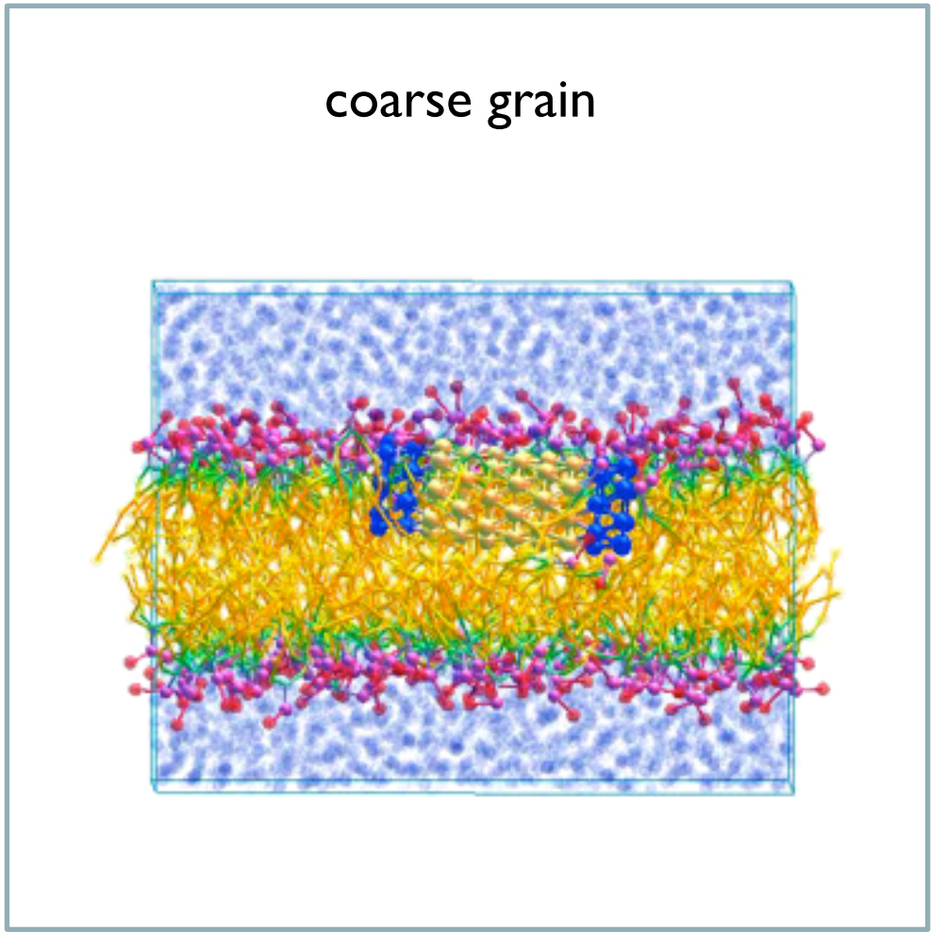
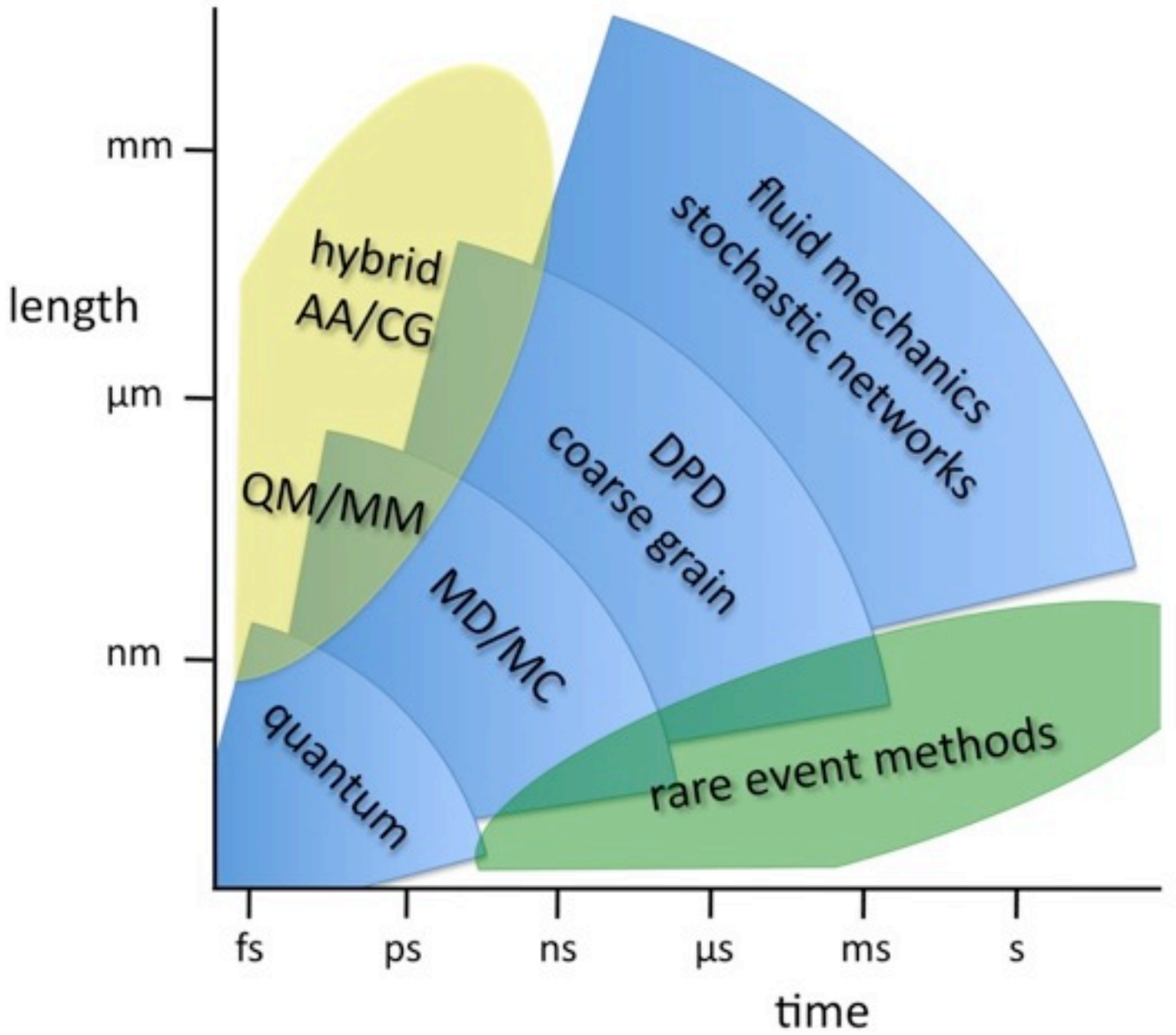


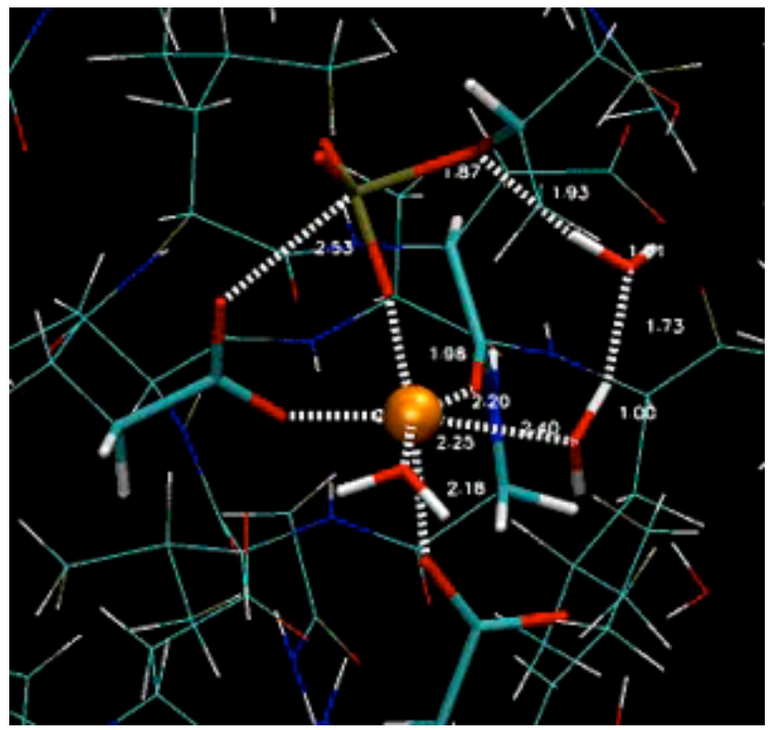




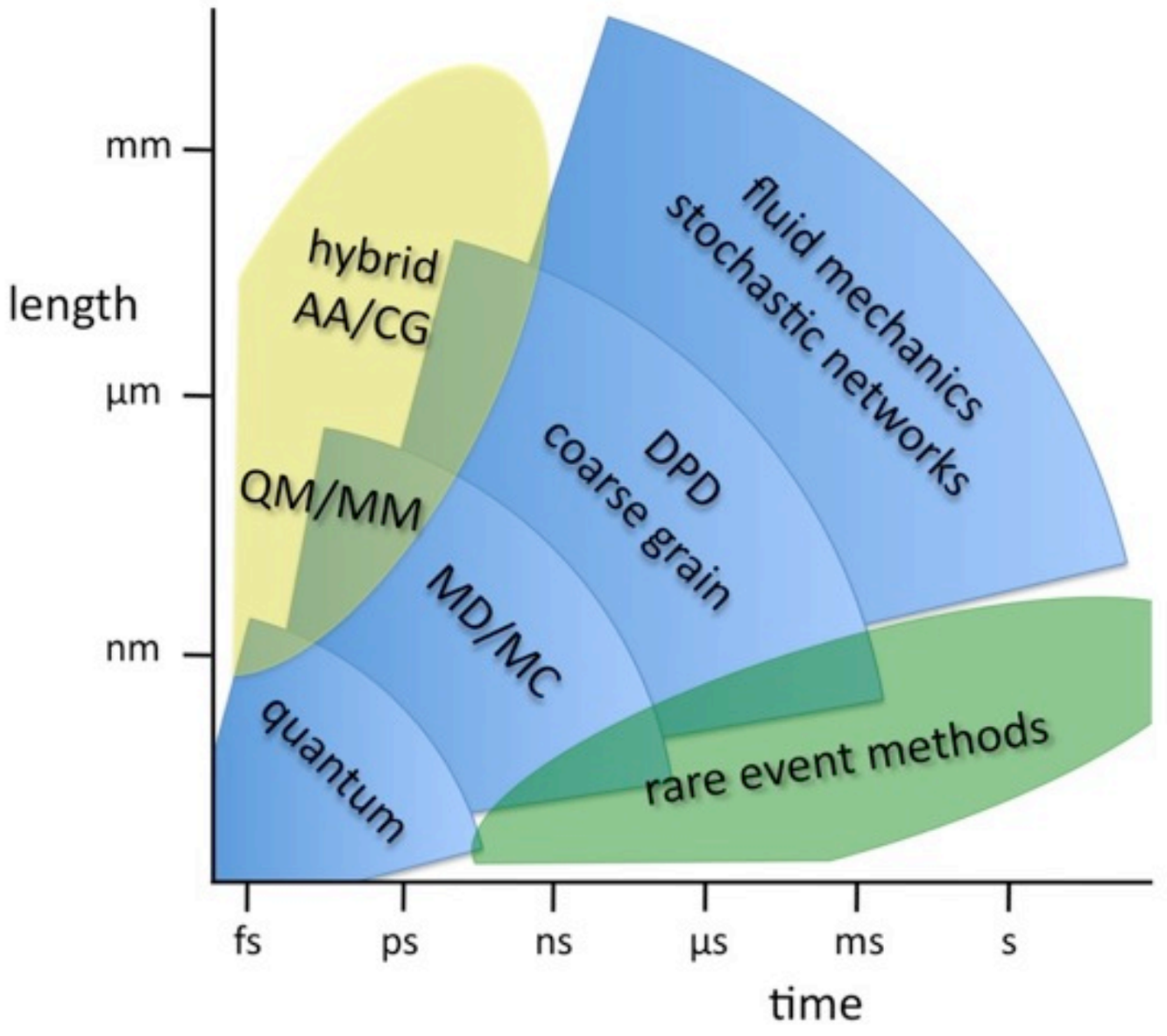
Spatial/Temporal scales in computational modeling



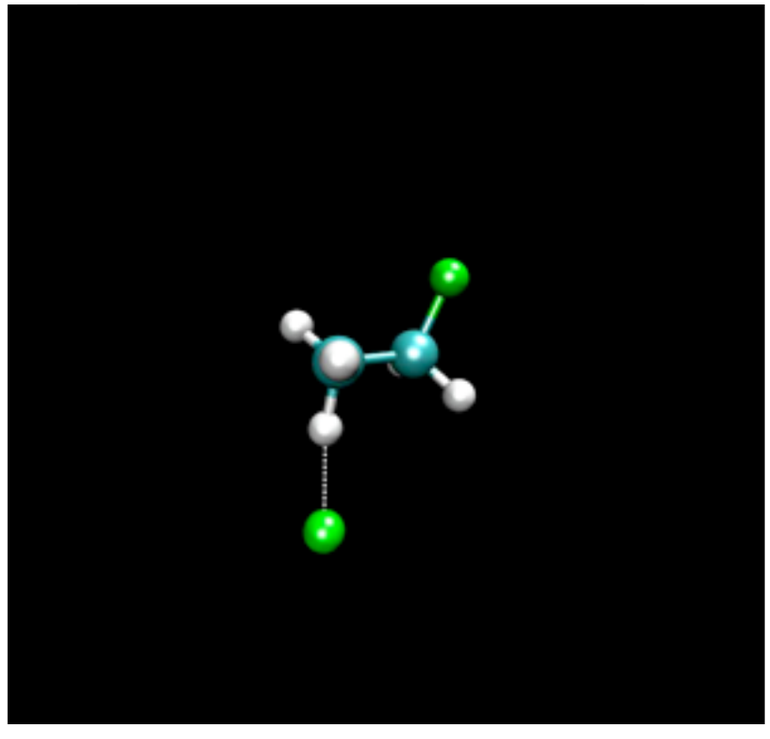
hybrid QM/MM



Spatial/Temporal scales in computational modeling

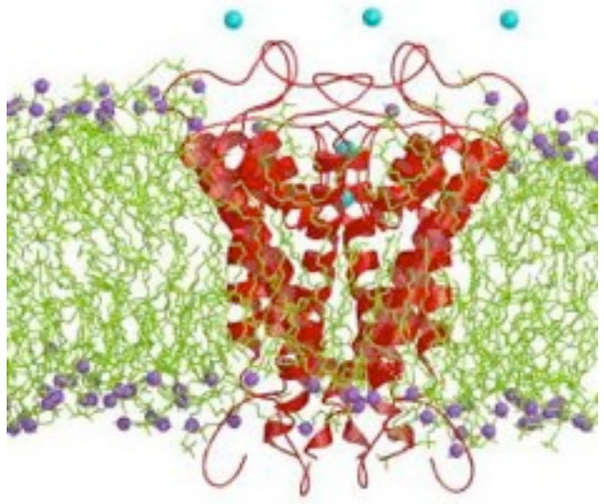


metadynamics

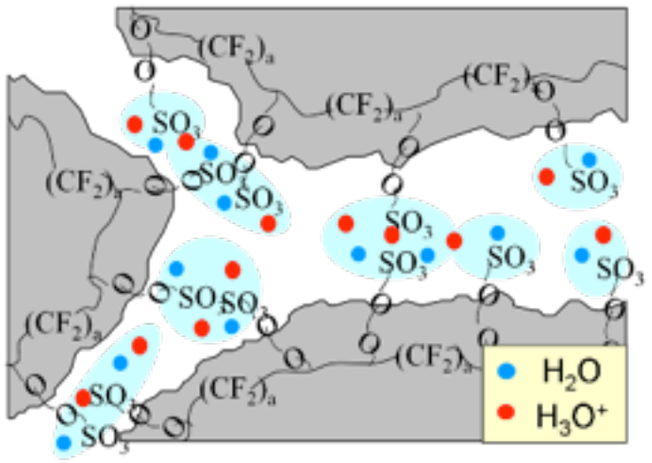


Multiscale systems

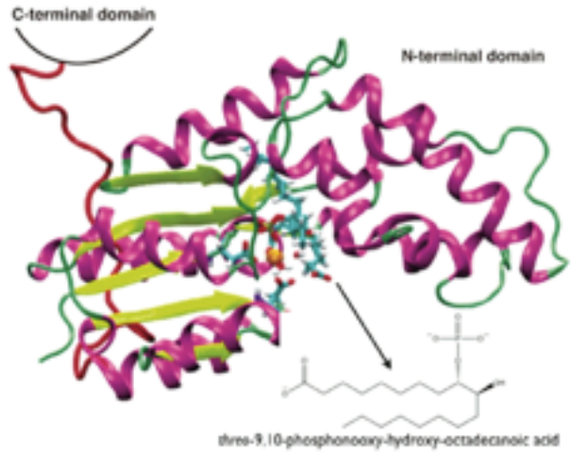
Molecular systems may exhibit phenomena on a range of scales in time, space or energy that are coupled to each other



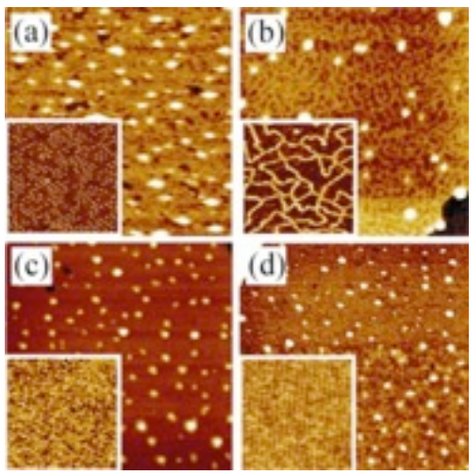
Potassium or proton transport channel



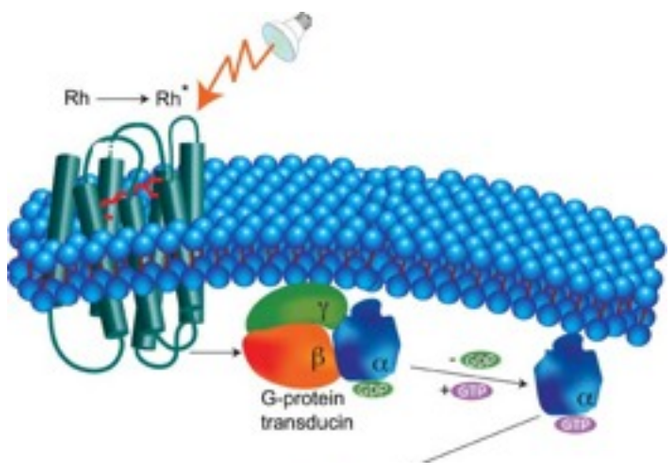
Ion and molecule diffusion in polyelectrolyte



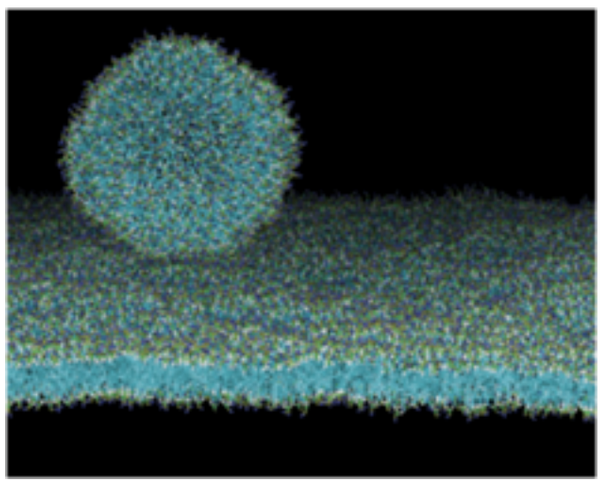
Enzymatic catalysis



Nanoparticle assembly on a drying surface



Signal transduction in G-coupled sensor proteins

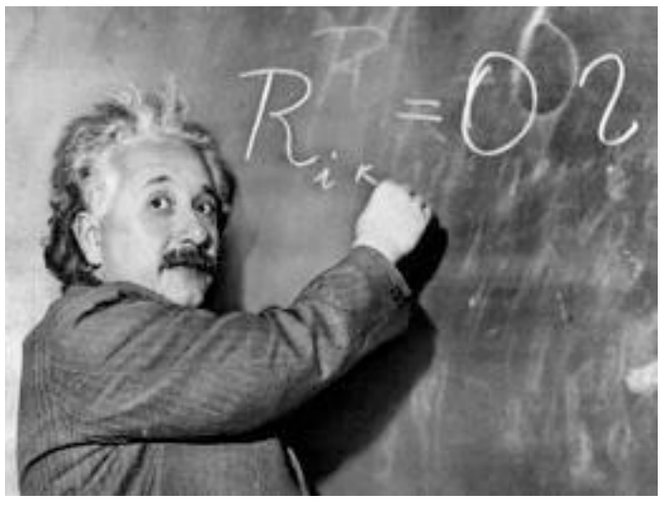


vesicle-membrane fusion

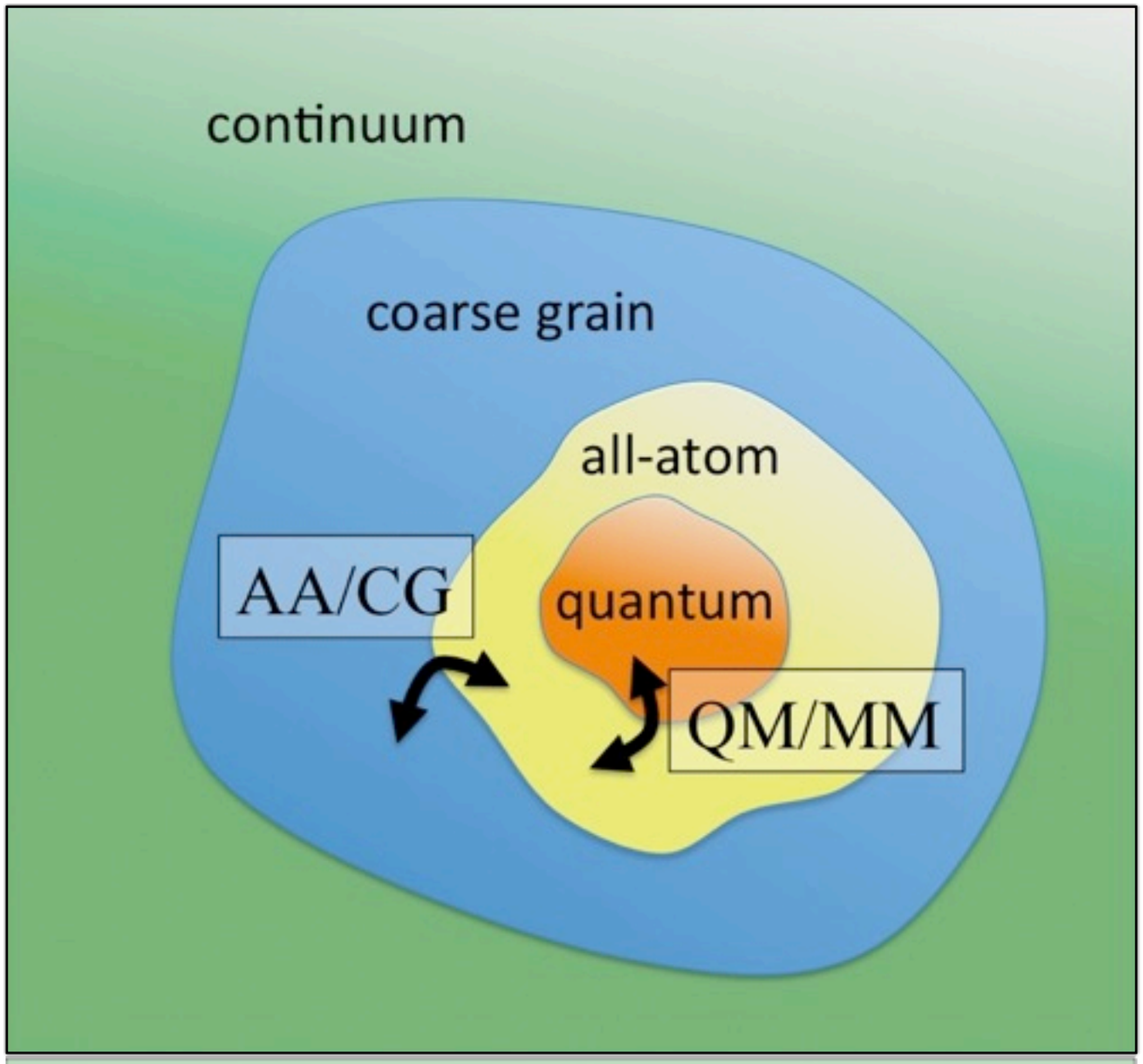
The Schrödinger equation cannot be solved for the entire system...

"Everything should be made as simple as possible, but not simpler."

"Everything should be made as simple as possible, but not simpler."



Multiscale methods



content

- Lecture 1: QM/MM
- Lecture 2: Density embedding
- Lecture 3: Coarse-graining
- Lecture 4: Hybrid multiscale molecular dynamics

Lecture I

QM/MM

J. Mol. Biol. (1976) 103, 227-249

QM/MM

Theoretical Studies of Enzymic Reactions: Dielectric, Electrostatic and Steric Stabilization of the Carbonium Ion in the Reaction of Lysozyme

A. WARSHEL AND M. LEVITT

Medical Research Council Laboratory of Molecular Biology
Hills Road, Cambridge CB2 2QH, England

and

Department of Chemical Physics
The Weixmann Institute of Science
Rehovot, Israel

(Received 12 September 1975, and in revised form 10 February 1976)

A general method for detailed study of enzymic reactions is presented. The method considers the complete enzyme-substrate complex together with the surrounding solvent and evaluates all the different quantum mechanical and classical energy factors that can affect the reaction pathway. These factors

QM/MM pioneers

Theoretical Studies of Enzymic Reactions: Dielectric, Electrostatic and Steric Stabilization of Reaction of Lysozyme the Carbonium Ion in the

A. Warshel AND M. Levitt

J. Mol. Biol. 103, 227-249 (1976)

A combined ab initio quantum mechanical and molecular mechanical method for carrying out simulations on complex molecular systems: Applications to the CH3Cl + Cl– exchange reaction and gas phase protonation of polyethers

U. Chandra Singh, Peter A. Kollman

J. Comput. Chem. 7, 718–730 (1986)

A combined quantum mechanical and molecular mechanical potential for molecular dynamics simulations

Martin J. Field, Paul A. Bash, Martin Karplus

J. Comput. Chem. 11, 700-733 (1990)

QM/MM

nature Vol 455|30 October 2008|doi:10.1038/nature07297

LETTERS

Low-speed fracture instabilities in a brittle crystal

J. R. Kermode[1], T. Albaret[2], D. Sherman[3], N. Bernstein[4], P. Gumbsch[5,6], M. C. Payne[1], G. Csányi[7] & A. De Vita[8,9]

When a brittle material is loaded to the limit of its strength, it fails by the nucleation and propagation of a crack[1]. The conditions for

for different cleavage planes. For a given cleavage plane, it can lead to slow crack growth[1,4,16] and anisotropy with respect to propagation

QM/MM

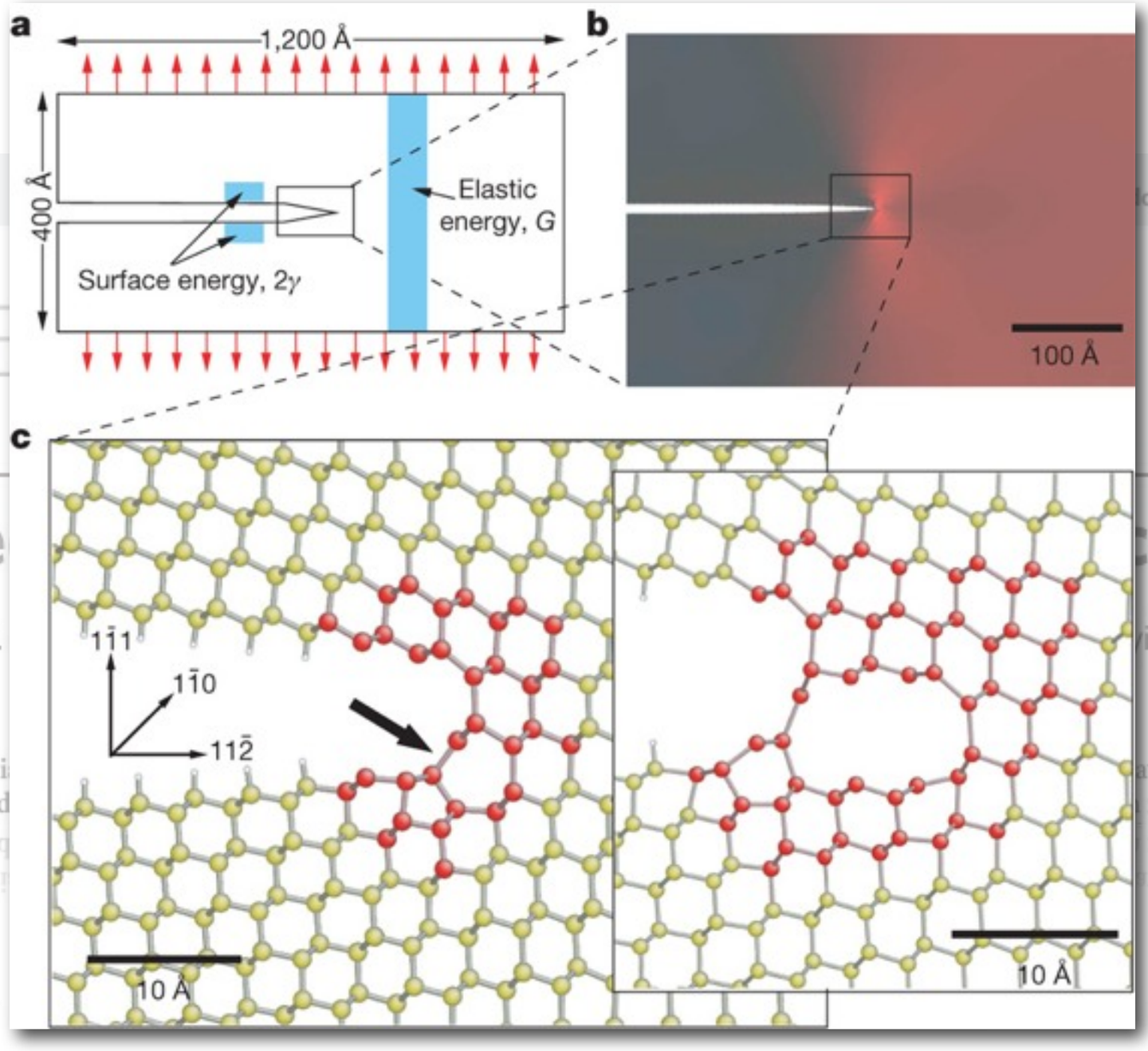
nature

LETTE

Low-spe

J. R. Kermode[1], T.

When a brittle materi
by the nucleation and



doi:10.1038/nature07297

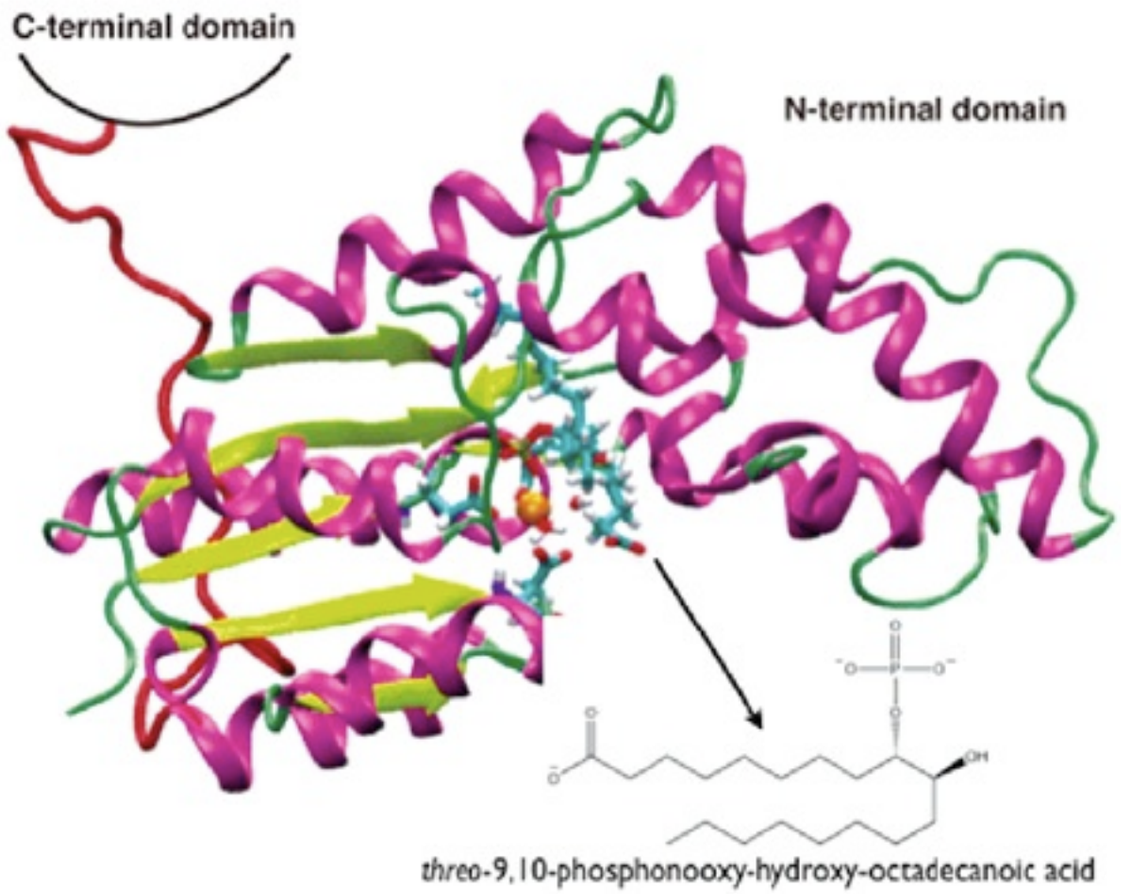
crystal

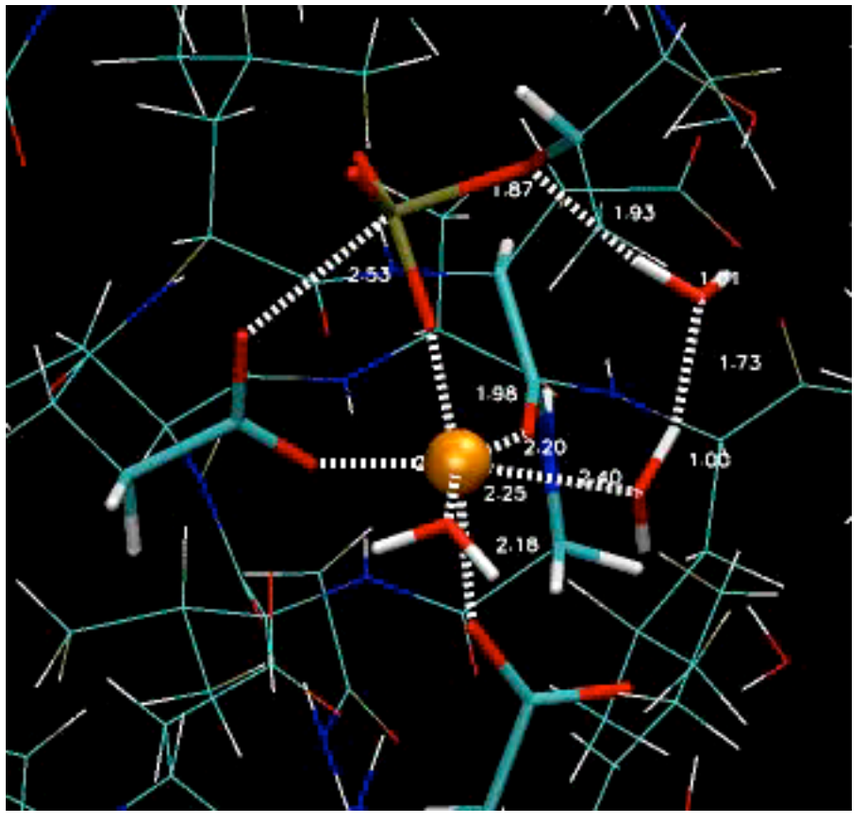
i[7] & A. De Vita[8,9]

avage plane, it can lead
respect to propagation

QM/MM

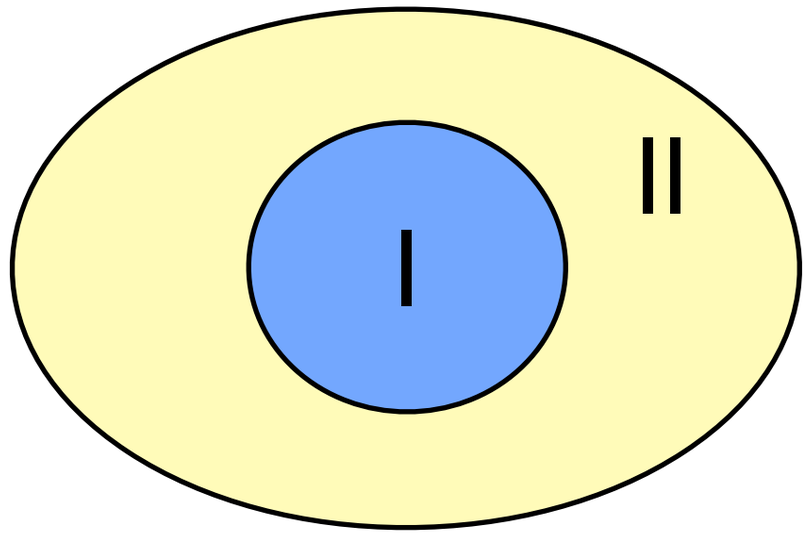
Proton Shuttles and Phosphatase Activity in Soluble Epoxide Hydrolase





QM/MM Energy function

Coupling between the QM and MM regions



I: QM
II: MM

$$E_{\mathrm{tot}} = E_{\mathrm{QM}}(I) + E_{\mathrm{MM}}(II)$$

$$E_{\mathrm{tot}} = E_{\mathrm{MM}}(I + II) + E_{\mathrm{QM}}(I) - E_{\mathrm{MM}}(I)$$

$$E_{\mathrm{tot}} = E_{\mathrm{QM}}(I) + E_{\mathrm{MM}}(II) + E_{\mathrm{QM-MM}}(I, II)$$

Electronic structure calculation

$$\hat{H}\psi = E\psi$$

Semi-empirical

Tight binding, AM1, PM3,...

Density Functional Theory

Hartree-Fock

MP2, CC, CI, CAS-PT2,...

Most QM/MM calculations use a semi-empirical approach for the QM part. The Car-Parrinello molecular dynamics community (CPMD, CP2K) uses DFT.

Kohn-Sham

$$E_0(\mathbf{R}) = \min_{\Psi_i} E_{\mathrm{KS}}[\Psi_i, \mathbf{R_i}]$$

$$\begin{aligned} E_{\mathrm{KS}}[\Psi_i, \mathbf{R_i}] &= \frac{1}{2}\sum_i \int d\mathbf{r}\, \psi_i^*(\mathbf{r})\nabla^2\psi_i(\mathbf{r}) + \int d\mathbf{r}\, V_N(\mathbf{r})\rho(\mathbf{r}) \\ &+ \frac{1}{2}\int d\mathbf{r}d\mathbf{r}'\, \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{\mathbf{r}-\mathbf{r}'} + E_{\mathrm{xc}}[\rho(\mathbf{r})] \end{aligned}$$

$$\rho(\mathbf{r}) = 2\sum_i \psi_i^*(\mathbf{r})\psi_i(\mathbf{r})$$

$$\int d\mathbf{r}\, \psi_i^*(\mathbf{r})\psi_j(\mathbf{r}) = \delta_{ij}$$

Molecular Mechanics

- Empirical Forcefield based on pair-wise potential functions
- Commonly used in classical molecular dynamics simulations
- MM2, AMBER, CHARMM, UFF, CFF, CVFF, GROMOS, OPLS,...

$$
\begin{aligned}
V_{\mathrm{MM}}(\mathbf{R}) &= \frac{1}{2}\sum_{N_b} k_b(b-b_0)^2 + \frac{1}{2}\sum_{N_a} k_a(a-a_0)^2 && \text{bonds + bends} \\
&+ \sum_{N_t} k_t[1+cos(mt-t_0)] + \frac{1}{2}\sum_{N_o} k_o(o-o_0)^2 && \text{dihedral + out-of-plane} \\
&+ \sum_{I}\sum_{J>I}\left(\frac{C_{12,IJ}}{R_{IJ}^{12}} - \frac{C_{6,IJ}}{R_{IJ}^{6}} + \frac{q_I q_J}{R_{IJ}}\right) && \text{Vanderwaals + electrostatics}
\end{aligned}
$$

... + Charge-Dipole
Dipole-Dipole

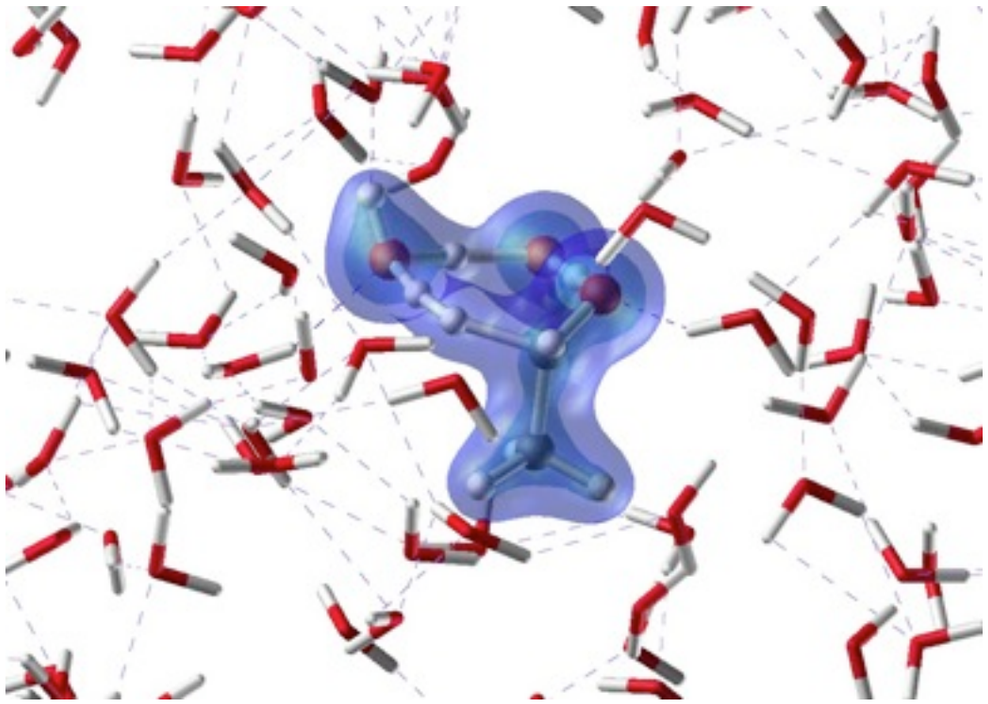
Coupling QM and MM

- Mechanical embedding only: bonds, angles, VdW
- Electrostatic embedding only: point charges-
- Electrostatic + mechanical

- QM system feels MM environment
- MM environment feels QM system via MM interactions
- MM environment feels QM system in a self-consistent manner

Electrostatic coupling

Electrostatic coupling is needed to include environment interaction in the QM system.
- polarization of electron density



- MM charges interact with electron density
  - can become a very large sum

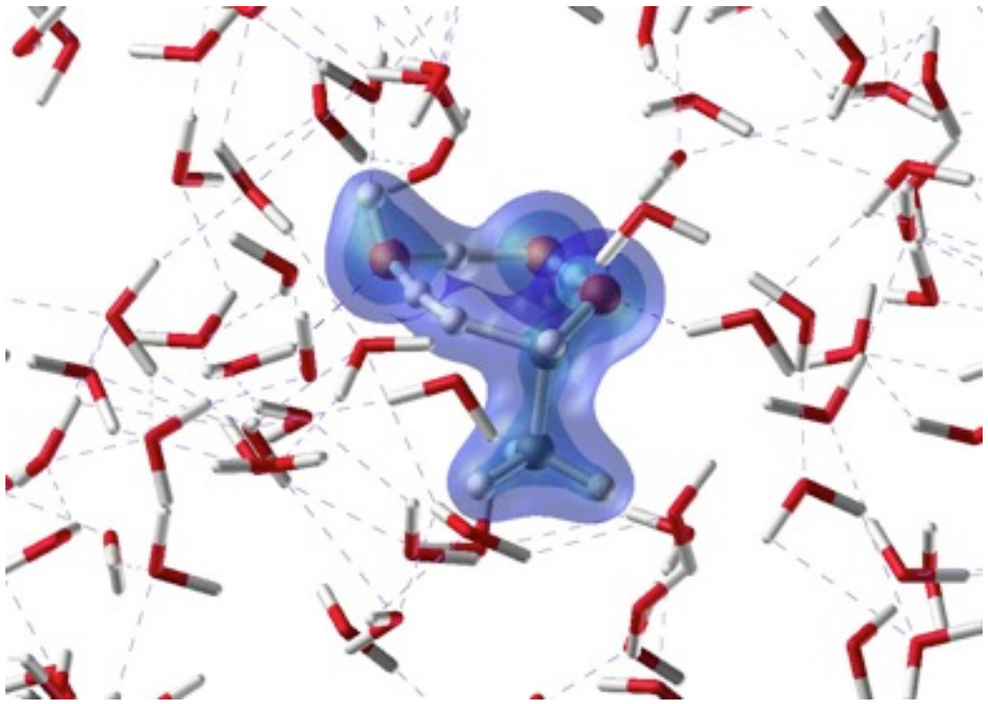
$$V_{\mathrm{QM/MM}} = \sum_{i \in \mathrm{MM}} q_i \int \frac{\rho_{\mathrm{QM}}(r)}{|r - r_i|} dr$$

- MM charges interact with QM charges
  - QM charges are obtained from density
  - but how? population analysis not rigorous
  - more efficient but more approximate

$$V_{\mathrm{QM/MM}} = \sum_{i \in \mathrm{MM}} \sum_{j \in \mathrm{QM}} \frac{q_i q_j(\rho_{\mathrm{QM}})}{|r_j - r_i|}$$

Electrostatic coupling

Electrostatic coupling is needed to include environment interaction in the QM system.
- polarization of electron density



No MM Pauli repulsion
- charge spilling into MM part
  - charge delocalization
  - MM pseudopotentials

MM multipole expansion

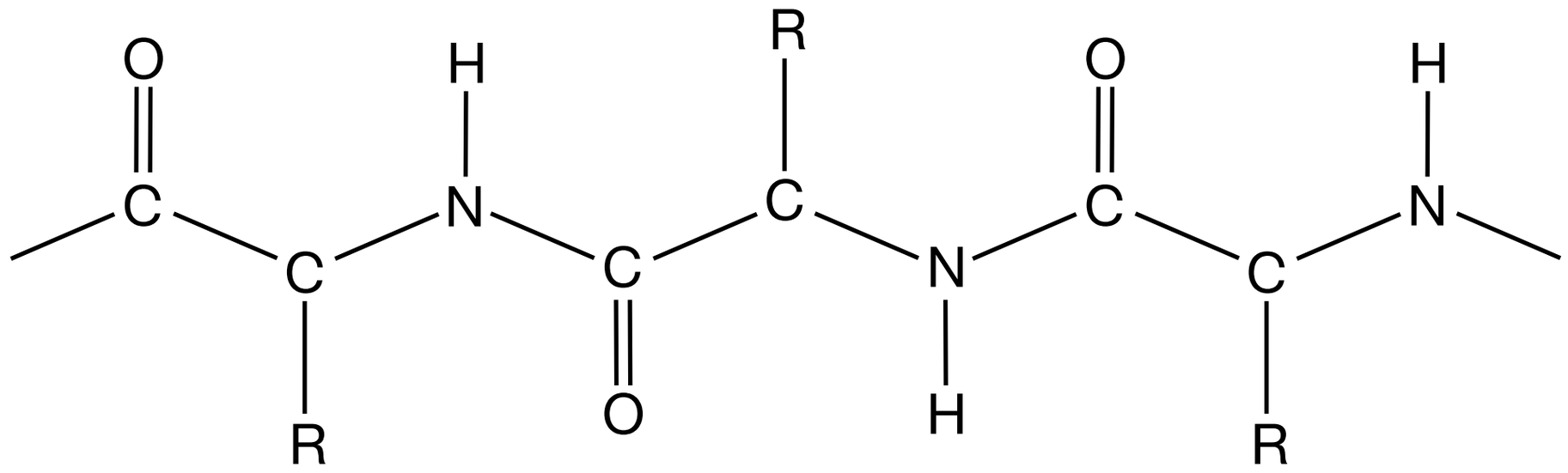
Polarization is one-way
  - polarizable forcefield

Periodic boundary conditions?
  - Ewald
  - Reaction Field

QM/MM partitioning

Cutting through chemical bonds: QM/MM bonds

Example: peptide chain



QM/MM partitioning

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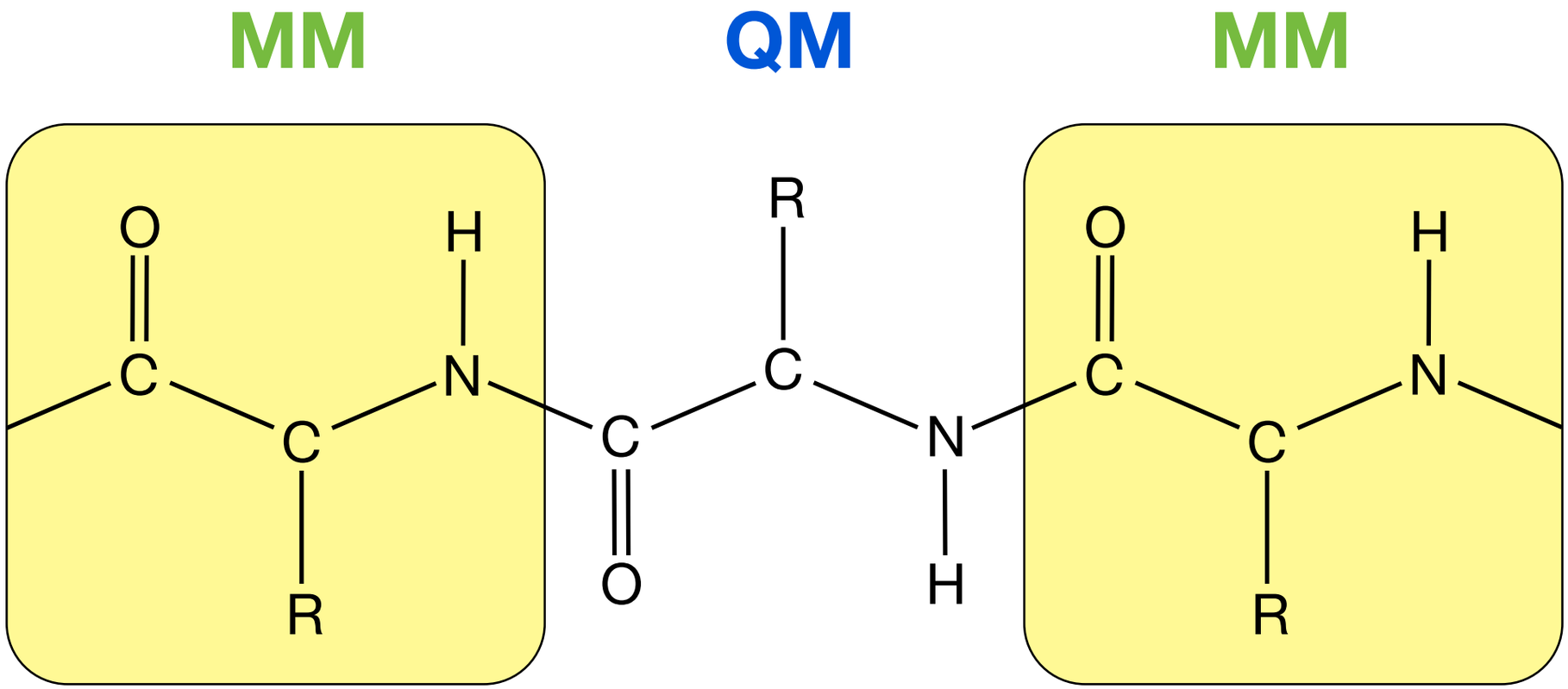
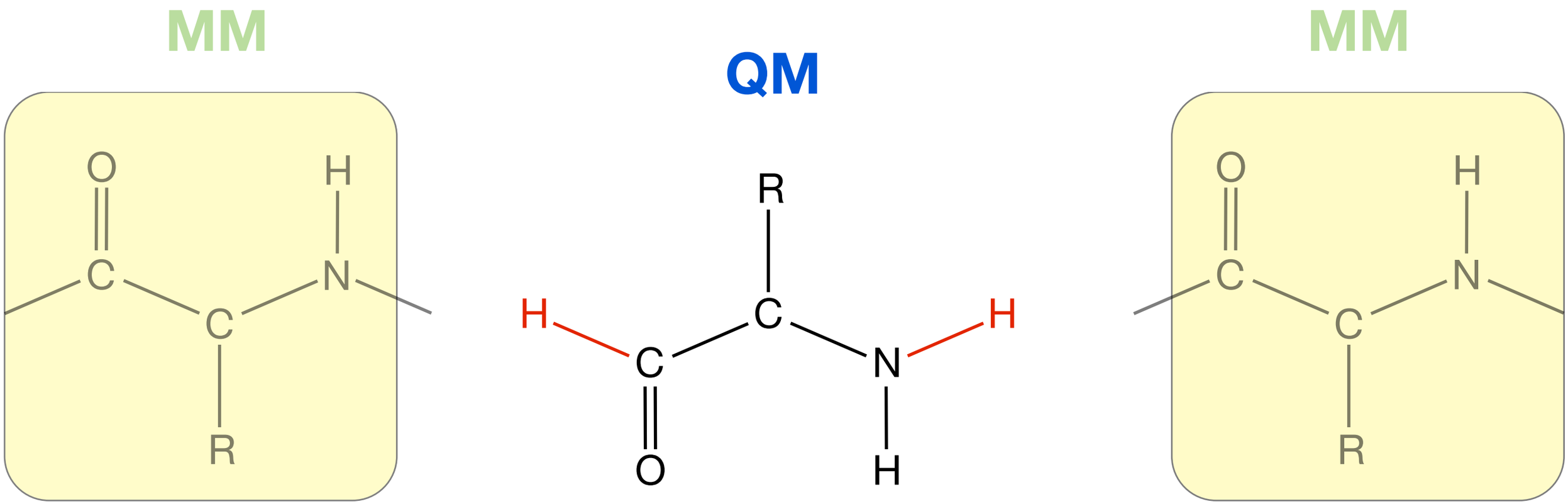


QM/MM partitioning

Cutting through chemical bonds: QM/MM bonds

Example: peptide chain



Add link atoms

- only seen by QM atoms?
- H, CH3, halogen atom
- Electronegativity of link atom should match MM part
- What about spectroscopy, excited states?

Or use frozen orbitals (“frozen bonds”)

Improving MM

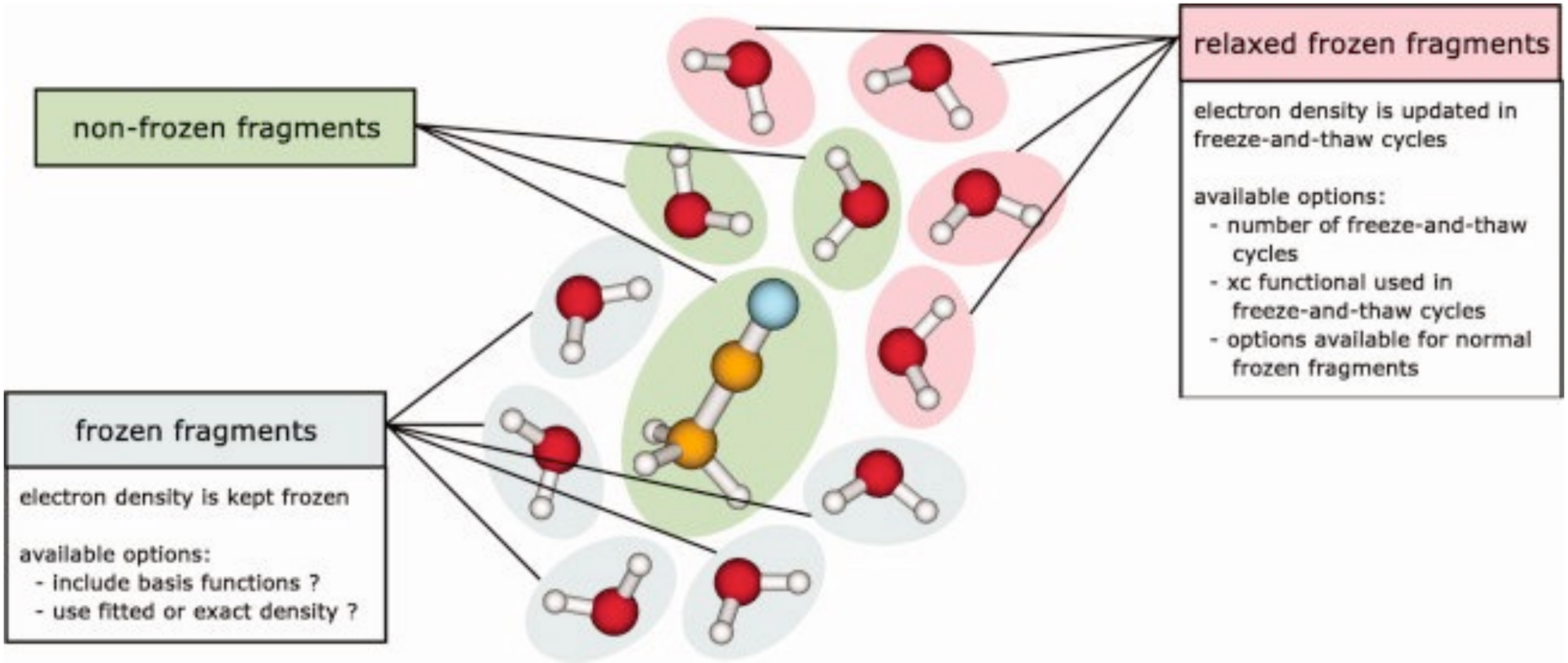
Force matching, fitting, learning on the fly,...

Lecture 2

Density Embedding

Frozen density embedding

T. A. Wesolowski, A. Warshel, *J. Phys. Chem.* **97**, 8050 (1993)
T. A. Wesolowski, In Computational Chemistry: Reviews of Current Trends, Vol. 10; Leszczynski, J., Ed.; World Scientific: Singapore, 2006.



Christoph R. Jacob, Johannes Neugebauer, Lucas Visscher
J. Comput. Chem. **29** 1011–1018 (2008)

Frozen density embedding

The total density is a sum of the densities ρ_I and ρ_{II} in different regions or subsystems

Density ρ_{II} of the environment is kept fixed
The total density $\rho_{tot} = \rho_I + \rho_{II}$ is obtained by optimizing ρ_I

KS-like equation with embedding term due to ρ_{II}

$$\left[-\frac{\nabla^2}{2} + V_{\text{eff}}^{\text{KS}}[\rho_{\text{I}}](\boldsymbol{r}) + V_{\text{eff}}^{\text{emb}}[\rho_{\text{I}}, \rho_{\text{II}}](\boldsymbol{r})\right]$$

$$\phi_i^{(\text{I})}(\boldsymbol{r}) = \varepsilon_i \phi_i^{(\text{I})}(\boldsymbol{r}), \quad i = 1, \ldots, N_{\text{I}}.$$

$$V_{\text{emb}}^{\text{eff}}[\rho_{\text{I}}, \rho_{\text{II}}](\boldsymbol{r}) = \sum_{A_{\text{II}}} -\frac{Z_{A_{\text{II}}}}{|\boldsymbol{r} - \boldsymbol{R}_{A_{\text{II}}}|} + \int \frac{\rho_{\text{II}}(\boldsymbol{r}')}{|\boldsymbol{r}' - \boldsymbol{r}|}\,\mathrm{d}\boldsymbol{r}'$$

$$+ \left.\frac{\delta E_{\text{xc}}[\rho]}{\delta\rho}\right|_{\rho=\rho_{\text{tot}}} - \left.\frac{\delta E_{\text{xc}}[\rho]}{\delta\rho}\right|_{\rho=\rho_{\text{I}}}$$

$$+ \left.\frac{\delta T_s[\rho]}{\delta\rho}\right|_{\rho=\rho_{\text{tot}}} - \left.\frac{\delta T_s[\rho]}{\delta\rho}\right|_{\rho=\rho_{\text{I}}},$$

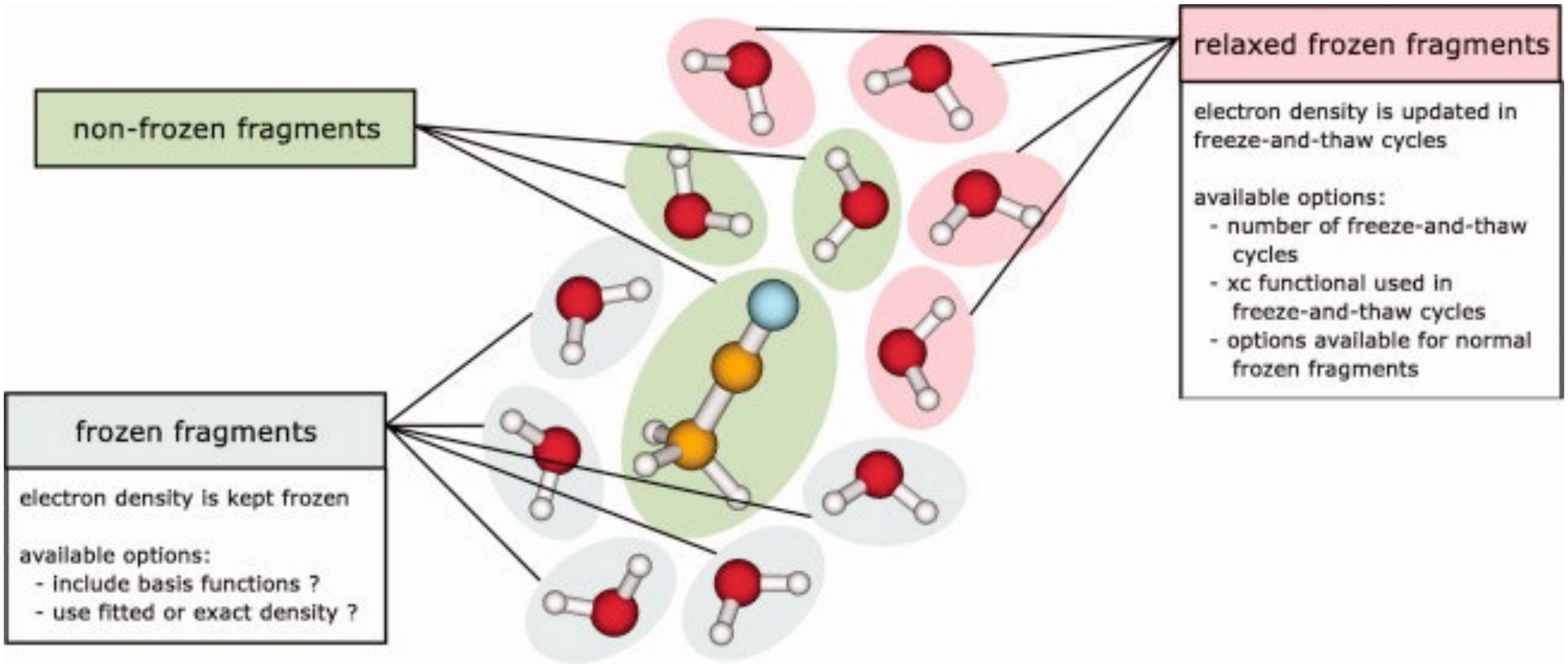
Embedding potential
- approximate kinetic energy functional (Thomas-Fermi, PW91k)
- accurate for weakly bound systems

non-additive kinetic energy functional $$T_s^{\text{nadd}}[\rho_{\text{I}}, \rho_{\text{II}}] = T_s[\rho_{\text{I}} + \rho_{\text{II}}] - T_s[\rho_{\text{I}}] - T_s[\rho_{\text{II}}]$$

If ρ_{tot} - ρ_{II} is positive definite and non-interacting v_s representable, the solution give exact ground-state.

Frozen density embedding

Acetonitrile and 15, 25, 40 water molecules



Christoph R. Jacob, Johannes Neugebauer, Lucas Visscher
J. Comput. Chem. **29** 1011–1018 (2008)

Frozen density embedding

Example application: NMR shifts for Acetonitrile-Water clusters

Table 1. Solvent Shifts $\Delta\sigma$ of the Nitrogen NMR Shielding in Acetonitrile–Water Clusters with 15, 25, and 40 Water Molecules, Respectively.

	15 H_2O $\Delta\sigma$ (ppm)		25 H_2O $\Delta\sigma$ (ppm)		40 H_2O $\Delta\sigma$ (ppm)	
Isolated	0.0		0.0		0.0	
SumFrag	12.6		11.9		11.8	
1 H_2O relaxed	12.9	+0.3	12.3	+0.4	11.9	+0.1
2 H_2O relaxed	13.3	+0.4	12.7	+0.4	12.4	+0.5
3 H_2O relaxed	13.7	+0.4	13.3	+0.6	13.1	+0.7
8 H_2O relaxed	14.6	+0.9	13.9	+0.6	14.0	+0.9
13 H_2O relaxed	15.3	+0.7	14.7	+0.8	14.7	+0.7
23 H_2O relaxed			15.2	+0.5	14.6	−0.1
38 H_2O relaxed					14.6	0.0
Supermolecule	14.0		13.1		12.5	

In the FDE calculations, the closest two water molecules have been included in the nonfrozen subsystem, for the remaining frozen fragments different approximations have been employed. For comparison, also the results of a conventional, supermolecular calculation are given. See text for details.

Frozen density embedding

Example application: NMR shifts for Acetonitrile-Water clusters

Table 2. Wall Clock Time (in Minutes) Required for the Calculation of the Nitrogen NMR Shielding in Acetonitrile–Water Clusters with 15, 25, and 40 Water Molecules, Respectively, on 8 Dual Processor Nodes of an Intel Xeon 3.4 GHz Cluster, Using Different Approximations for the Frozen Density (see text for details).

	15 H_2O	25 H_2O	40 H_2O
Isolated	0.4	0.4	0.4
SumFrag	1.7	2.1	2.9
1 H_2O relaxed	2.6	3.1	4.3
2 H_2O relaxed	2.8	3.6	5.0
3 H_2O relaxed	3.0	3.8	5.0
8 H_2O relaxed	3.6	5.2	6.2
13 H_2O relaxed	4.0	5.3	7.2
23 H_2O relaxed		7.1	9.4
38 H_2O relaxed			12.8
Supermolecule	8.5	29.8	103.5

Polarizable QM/MM

Discreet reaction field model

Solvent is represented by charges q_s and polarizabilities α_s places at positions $\mathbf{r}_s$

Kohn-Sham like equations

$$\left[-\frac{\nabla^2}{2} + V_{\text{eff}}^{\text{KS}}[\rho](\boldsymbol{r}) + V^{\text{DRF}}[\rho](\boldsymbol{r})\right]\phi_i(\boldsymbol{r}) = \varepsilon_i\phi_i(\boldsymbol{r})$$
$$i = 1, \ldots, N.$$

with a Coulomb term due to permanent charges and a many-body polarization term:

$$V^{\text{DRF}}[\rho](\boldsymbol{r}) = V^{\text{el}}(\boldsymbol{r}) + V^{\text{pol}}[\rho](\boldsymbol{r})$$
$$= \sum_s \frac{q_s}{|\boldsymbol{r} - \boldsymbol{R}_s|} + \sum_s \boldsymbol{\mu}_s^{\text{ind}} \cdot \frac{(\boldsymbol{r} - \boldsymbol{R}_s)}{|\boldsymbol{r} - \boldsymbol{R}_s|^3}$$

The MM induced atomic dipole:

$$\mu_s^{\text{ind}} = \alpha_s \left[\mathrm{F}_s^{\text{init}} + \sum_{t,t\neq s} \boldsymbol{T}_{st}^{(2)}\, \boldsymbol{\mu}_t^{\text{ind}}\right]$$

with **T** the screened dipole interaction tensor of interaction between sites.
Field **F** at site s is due to QM charge distribution, QM nuclei, MM charges, MM dipoles.
Self-consistent procedure!

B. T. Thole and P. Th. van Duijnen, *Theor. Chim. Acta* **55** 307–318 (1980)

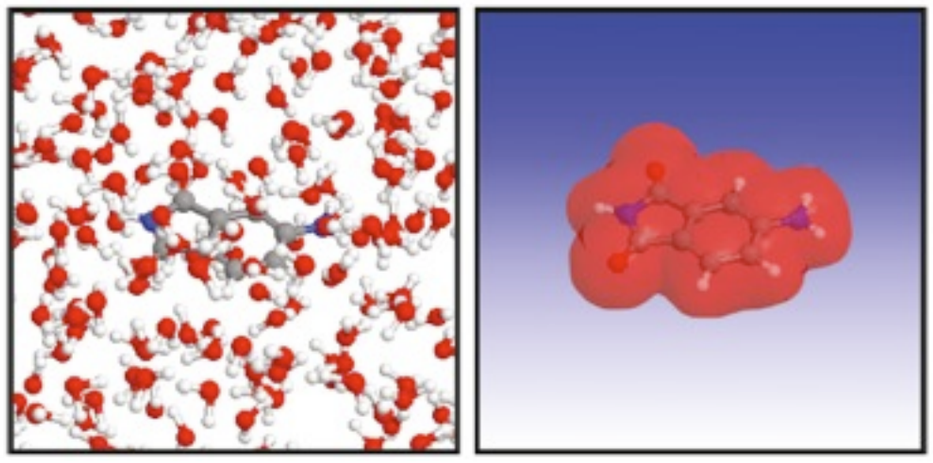
Implicit solvent models

Polarizable Continuum Model (C-PCM, D-PCM)

COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient
S. Miertus, E. Scrocco, J. Tomasi, *Chem. Phys.* **55**, 117 (1981).
R. Cammi, J. Tomasi, *J. Comput. Chem.* **16**, 1449 (1995).

Continuum Solvation model (COSMO)

COSMO: a new approach to dielectric screening in solvents with explicit expressions for the screening energy and its gradient
A. Klamt and G. Schüürmann
J. Chem. Soc., Perkin Trans. ***2***, 1993, 799-805



Reviews:

C. J. Cramer and D. G. Truhlar, *Chem. Rev.* **99,** 2161-2200 (1999)
J. Tomasi, B. Mennucci and R. Cammi, *Chem. Rev.* **105,** 2999-3094 (2005)

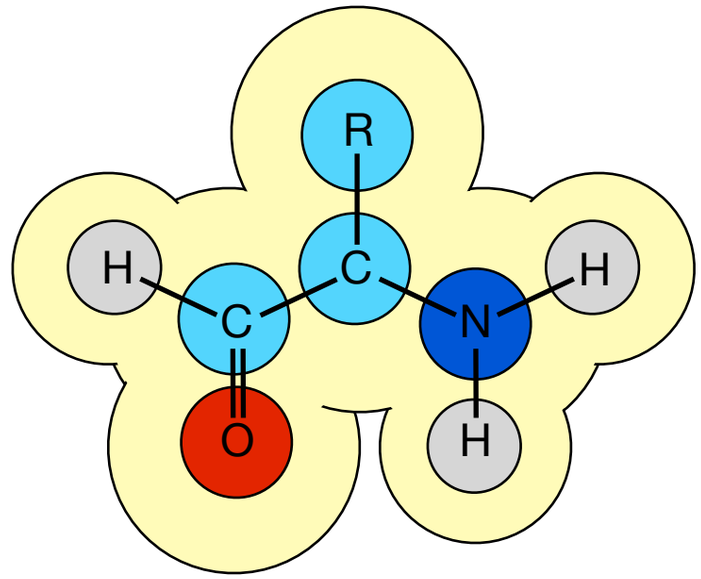
Implicit solvent models

Solute molecule in continuous solvent

Based on Onsager's reaction field method

- Solute is treated explicitly at QM level
- Only electrostatic solvent-solute interactions

- Solute is placed in a void cavity
  - shape of cavity is important; different methods
  - should contain most of solute electron density
  - should exclude the solvent
  - e.g. iso-density surface
  - or iso-energy surface (with He/Ar atom), SAS
  - or simply van der Waals radii
- Solvent is represented by continuous dielectric medium



- Charge distribution of the solute, inside the cavity, polarizes the dielectric continuum, which in turn polarizes the solute charge distribution

$$-\nabla^2 V(\vec{r}) = 4\pi\rho_{\mathrm{M}}(\vec{r}) \quad \text{within } C$$

$$-\epsilon\nabla^2 V(\vec{r}) = 0 \quad \text{outside } C$$

Summary QM/MM

Many algorithms and implementations available

QSite, Jaguar program, Schrödinger
QM: Hartree Fock, DFT, MP2

GROMACS-CPMD (Rothlisberger)
QM: DFT/plane-waves

QMMM Minnesota, (Truhlar)
QM package: GAMESS, Gaussian, ORCA + MM package: TINKER

ChemShell TCL interface (Daresbury)
Combines: GAMESS-UK, DL_POLY, MNDO97, TURBOMOLE, CHARMM, GULP, Gaussian94

ONION, IMOMM (Morokuma)
also in ADF: DFT + Amber/Sybyl forcefields

QM/MM can not (yet) be used as a black box method
- many parameters
- quality of QM model, MM model
- quality of QM/MM coupling
- be careful: for every approach a situation can be concocted such that it will fail