Chimica Computazionale

Hybrid multiscale schemes

Emanuele Coccia

UNIVERSITÀ DEGLI STUDI DI TRIESTE

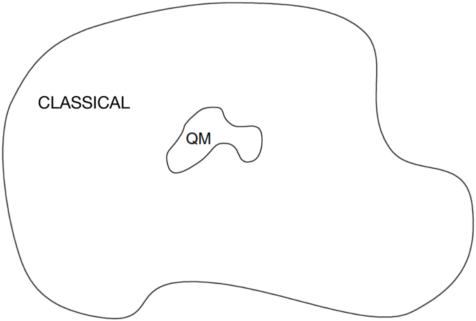
DSCF Dipartimento di Scienze Chimiche e Farmaceutiche

PhotoInduced Quantum Dynamics (PIQD) Group

PIQD

Hybrid multiscale methods

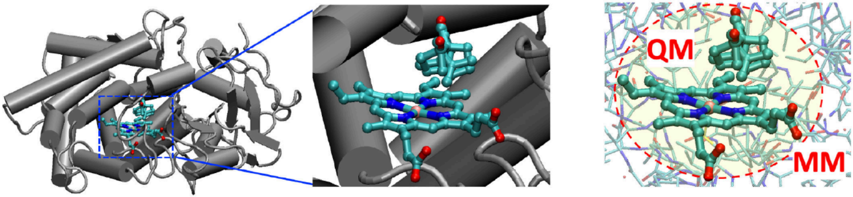
- Physical and chemical properties in large systems (10^4-10^6 atoms) → quantum (QM) methods not applicable
- Quantum meets classical:
  - QM for a (small) subregion of the system
  - Classical for the rest of it (environment)



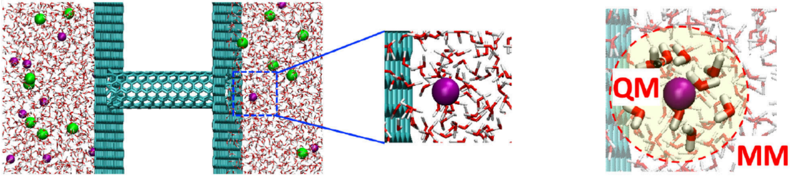
Hybrid multiscale methods

Biological/biochemical applications

ENZYMATIC CATALYSIS



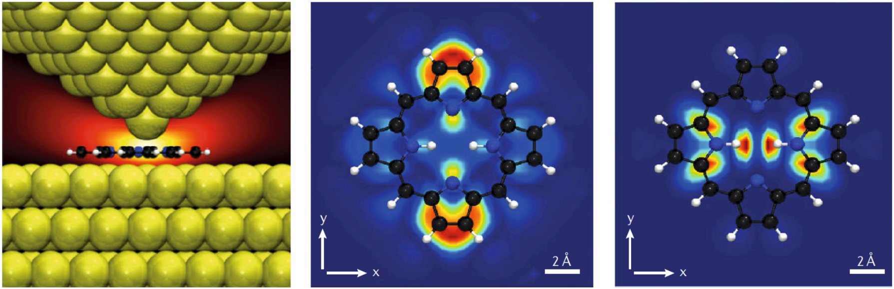
ION CHANNELS



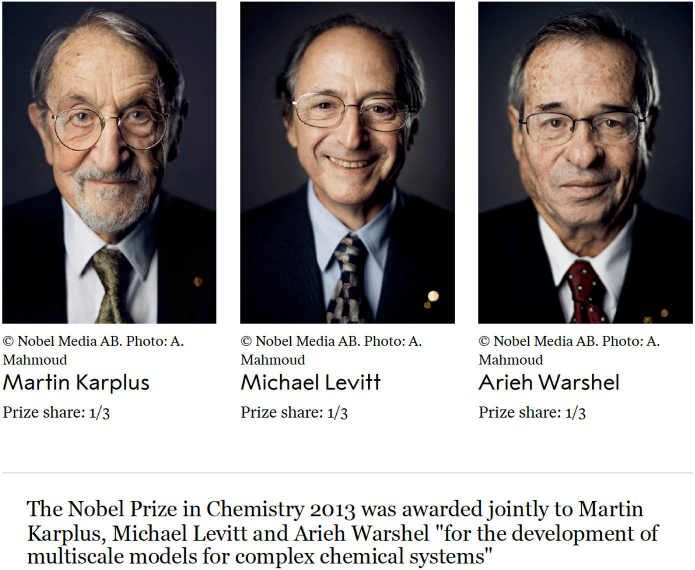
Hybrid multiscale methods

Materials applications

METAL-ENHANCED SPECTROSCOPIES



Nobel prize in Chemistry 2013



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Martin Karplus

Prize share: 1/3

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Michael Levitt

Prize share: 1/3

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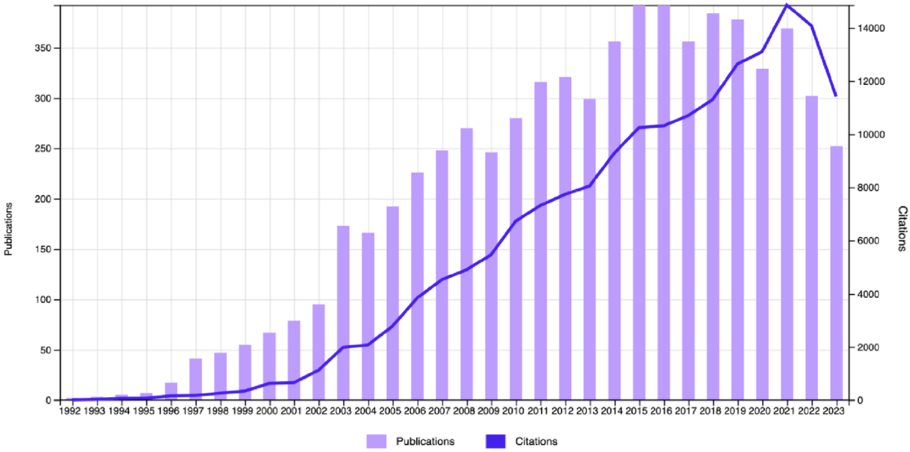
Arieh Warshel

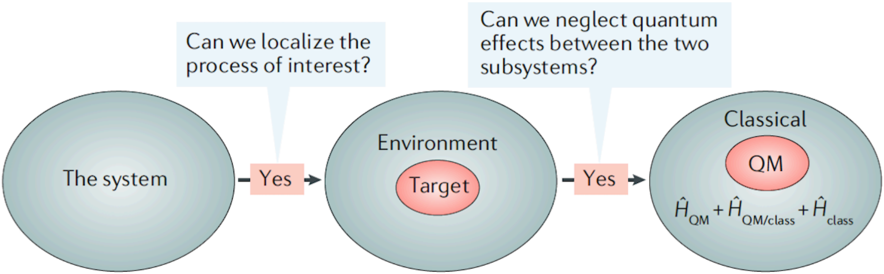
Prize share: 1/3

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel "for the development of multiscale models for complex chemical systems"

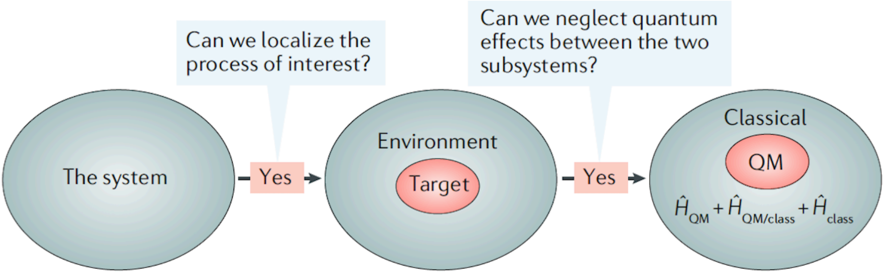
Hybrid multiscale methods



Hybrid multiscale methods

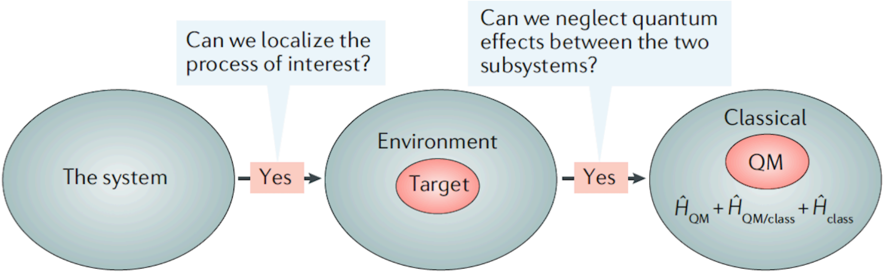


Hybrid multiscale methods



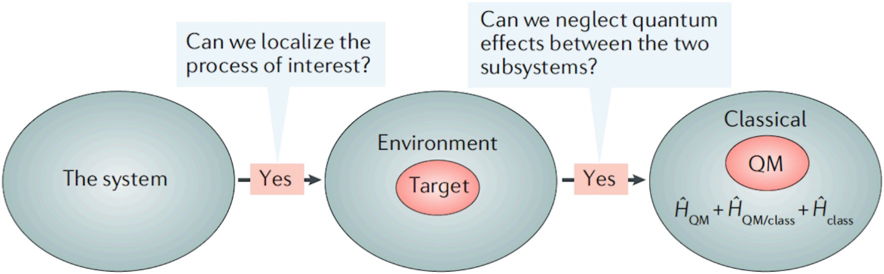
- How the classical part is modelled?

Hybrid multiscale methods



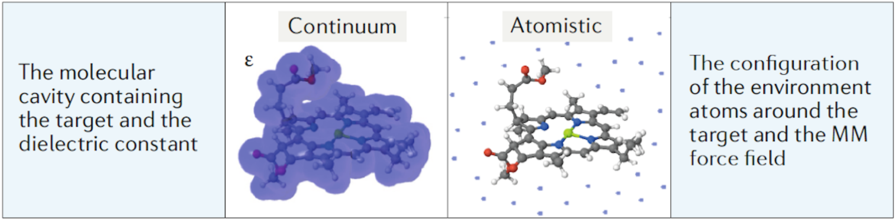
- How the classical part is modelled?
- How partition is done?

Hybrid multiscale methods



- How the classical part is modelled?
- How partition is done?
- How QM and classical subregions interact?

Modelling the classical environment



The molecular cavity containing the target and the dielectric constant

The configuration of the environment atoms around the target and the MM force field

- Atomistic: use force fields from molecular mechanics (MM)
- Continuum: the environment is a polarizable medium

Partitioning the system

- Local character of most chemical reactions in condensed phases
- Distinction between a "reaction center" and a "spectator"
- Expensive but accurate QM for the small "reaction center"
- Cheaper classical methods for the "spectator" region

Partitioning the system

- Local character of most chemical reactions in condensed phases
- Distinction between a “reaction center” and a “spectator”
- Expensive but accurate QM for the small “reaction center”
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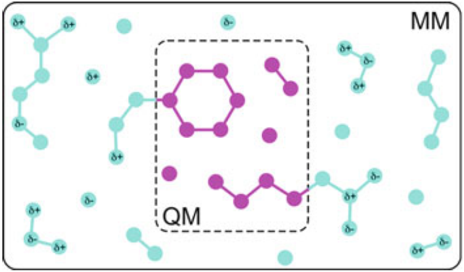
- Try to avoid to cut bonds at the boundaries
- But this too is covered by the models (see next slides)

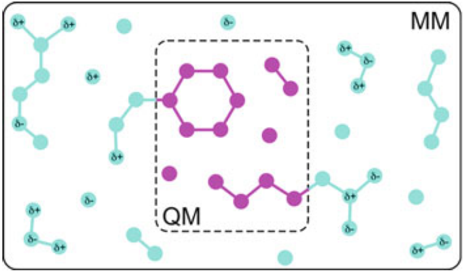
QM/MM methods

QM/MM



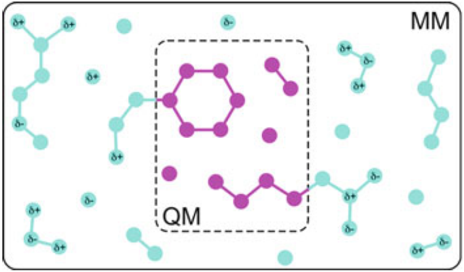
- Three types of interaction:

QM/MM



- Three types of interaction:
  - Among atoms in the QM region

QM/MM



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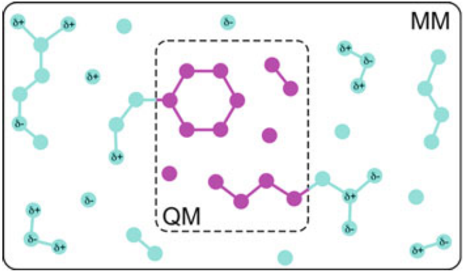
QM/MM



- Three types of interaction:
  - Among atoms in the QM region
  - Among atoms in the MM region (electrons ignored in the MM region!)
  - Among QM and MM atoms ←

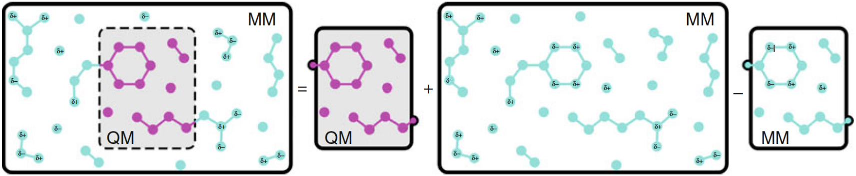
QM/MM

- $E_{QM/MM}$(QM/MM): coupling energy between QM and MM subregions

QM/MM

- $E_{QM/MM}$(QM/MM): coupling energy between QM and MM subregions
- Subtractive QM/MM coupling

$$E_{QM/MM}(\mathrm{QM/MM}) = E_{MM}(\mathrm{full}) + E_{QM}(\mathrm{QM}) - E_{MM}(\mathrm{QM})$$



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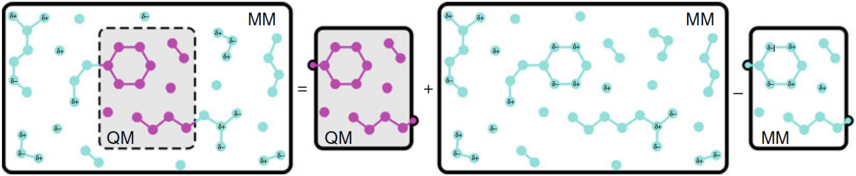

- Advantage:
  - Straightforward implementation (no QM/MM communication)

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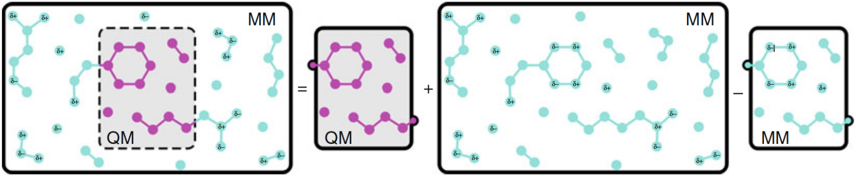


- Advantage:
  - Straightforward implementation (no QM/MM communication)

  Drawbacks:
  - Required force field for QM subregion
  - No polarization of the QM electron density by MM environment

QM/MM

- Additive QM/MM coupling

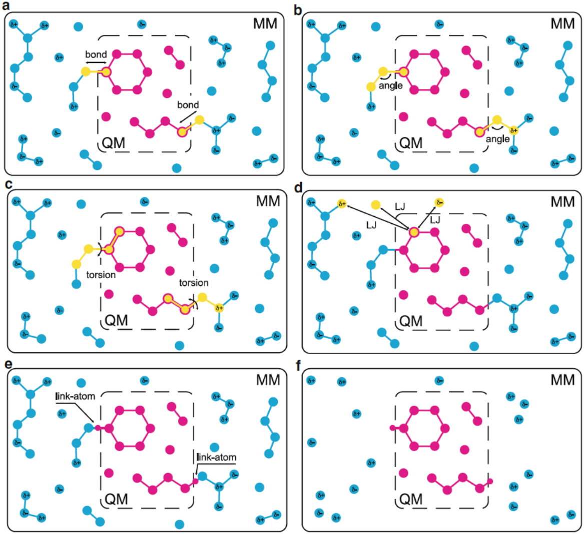
$$\hat{H}_{\text{full}}(\text{full}) = \hat{H}_{QM}(\text{QM}) + \hat{H}_{MM}(\text{MM}) + \hat{H}_{QM/MM}(\text{QM/MM})$$

- MM region only at classical level
- $E_{QM/MM}$(QM/MM) explicitly computed
  - Mechanical embedding
  - Electrostatic embedding

$$\begin{aligned} E_{QM/MM} &= E_b + E_{nb} \\ E_b &= E_{bond} + E_{angle} + E_{dihe} \\ E_{nb} &= E_{VdW} + E_{el} \end{aligned}$$

QM/MM

Mechanical embedding



QM/MM

$$\hat{H}_{QM/MM} = \hat{H}_b + \hat{H}_{nb}$$

QM/MM

$$\begin{aligned}
\hat{H}_{QM/MM} &= \hat{H}_b + \hat{H}_{nb} \\
\hat{H}_b &= \sum_k^{QM\ atoms} \sum_m^{MM\ atoms} E_{bond}(r_{km}) \\
&+ \sum_{k,m,l} E_{angle}(\theta_{kml}) \\
&+ \sum_{k,m,l,p} E_{dihe}(\theta_{kmlp})
\end{aligned}$$

QM/MM

$$
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\hat{H}_b &= \sum_{k}^{QM\ atoms} \sum_{m}^{MM\ atoms} E_{bond}(r_{km}) \\
&+ \sum_{k,m,l} E_{angle}(\theta_{kml}) \\
&+ \sum_{k,m,l,p} E_{dihe}(\theta_{kmlp}) \\
\hat{H}_{nb} &= \sum_{k}^{QM\ atoms} \sum_{m}^{MM\ atoms} \left[\frac{Z_k q_m}{r_{km}} + 4\epsilon_{km} \left(\frac{\sigma_{km}^{12}}{r_{km}^{12}} - \frac{\sigma_{km}^{6}}{r_{km}^{6}} \right) \right]
\end{aligned}
$$

QM/MM

- Electrostatic embedding: polarization included

$$\hat{H}_{nb,el} = \hat{H}_{nb} - \sum_{i}^{electrons} \sum_{m}^{MM\ atoms} \frac{q_m}{r_{im}}$$

QM/MM

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- Electrons see MM atoms as special nuclei with non-integer and possibly negative charges

QM/MM

- Electrostatic embedding: polarization included

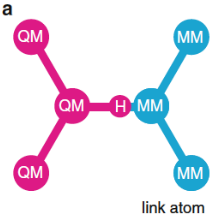
$$\hat{H}_{nb,el} = \hat{H}_{nb} - \sum_i^{electrons} \sum_m^{MM\ atoms} \frac{q_m}{r_{im}}$$

- Electrons see MM atoms as special nuclei with non-integer and possibly negative charges
- Risk of overpolarization at boundaries (electron spill-out)
- Smeared charges

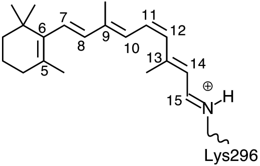
$$\Omega_m(r) = \sqrt{\frac{q_m}{\pi\alpha^3}} \exp\left[\frac{(r - r_m)^2}{2\alpha^2}\right]$$

QM/MM

- Capping bonds at the QM/MM boundary
- Monovalent link atom at an appropriate position along the bond vector between the QM and MM atoms



- Link atom only present in the QM calculation
- Link atom frozen at a given position
- Do not cut double or triple bonds



QM/MM

$$
\begin{aligned}
\langle\Psi|\hat{H}_{\mathrm{full}}|\Psi\rangle &= \langle\Psi|\hat{H}_{\mathrm{QM}}|\Psi\rangle + \langle\Psi|\hat{H}_{\mathrm{MM}}|\Psi\rangle + \langle\Psi|\hat{H}_{\mathrm{QM/MM}}|\Psi\rangle \\
&= \langle\Psi| - \sum_i^N \frac{1}{2}\nabla_i^2 - \sum_i^N \sum_k^K \frac{Z_k}{r_{ik}} + \sum_{i<j} \frac{1}{r_{ij}} + \sum_{k<l} \frac{Z_k Z_l}{r_{kl}} |\Psi\rangle \\
&+ \langle\Psi|\Psi\rangle E_{MM} + \langle\Psi| - \sum_i^N \sum_m^M \frac{q_m}{r_{im}} |\Psi\rangle + \langle\Psi|\Psi\rangle \left(E_b + E_{nb}\right)
\end{aligned}
$$

QM/MM

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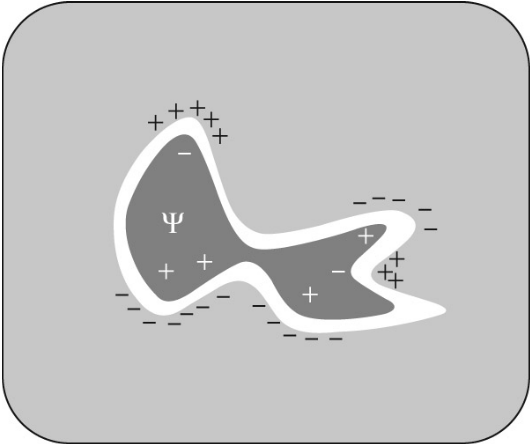
&= \langle\Psi| - \sum_i^N \frac{1}{2}\nabla_i^2 - \sum_i^N\sum_k^K \frac{Z_k}{r_{ik}} - \sum_i^N\sum_m^M \frac{q_m}{r_{im}} + \sum_{i<j}\frac{1}{r_{ij}} + \sum_{k<l}\frac{Z_kZ_l}{r_{kl}}|\Psi\rangle \\
&+ E_{MM} + E_b + E_{nb}
\end{aligned}$$

SCF calculation affected by the MM charges

Polarizable continuum models

QM/continuum

- Continuum models for solutions
- QM solute(s), solvent as a polarizable medium



- Medium with a dielectric constant ϵ

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$$\Delta G_{\text{solv}} = \Delta G_{\text{cavity}} + \Delta G_{\text{dispersion}} + \Delta G_{\text{elec}}$$

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  - how size and shape of the hole are defined

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- ϵ fully describes the solvent
- Also spatial and frequency dependencies are used, i.e. $\epsilon(\mathbf{r})$ and $\epsilon(\omega)$

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- Interlocking spheres on each nucleus (vdW surface)

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- Interlocking spheres on each nucleus (vdW surface)
- Born model

$$\Delta G_{\text{solv}} = -\frac{1}{2}\left(1 - \frac{1}{\epsilon}\right)\frac{q^2}{r}$$

QM/continuum

- Self-consistent reaction field (SCRF)
- Poisson equation (electrostatic potential ϕ, solute charge distribution ρ)

$$\nabla \cdot (\epsilon(\mathbf{r})\nabla\phi(\mathbf{r})) = -4\pi\rho(\mathbf{r})$$

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\end{aligned}$$

- Extra term in the Hamiltonian

$$\begin{aligned}
\hat{H}_{\mathrm{SCRF}} &= \hat{H} + \phi_\sigma \\
\phi_\sigma(\mathbf{r}) &= \int \frac{\sigma(\mathbf{r}_s)}{|\mathbf{r} - \mathbf{r}_s|} d\mathbf{r}_s
\end{aligned}$$

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QM/continuum

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$$\phi(\mathbf{r}) = \phi_{\text{nuc}}(\mathbf{r}) + \phi_{\text{el}}(\mathbf{r}) + \phi_{\text{pol}}(\mathbf{r})$$

QM/continuum

- Mixed solvent models
- First solvation shell explicitly modelled

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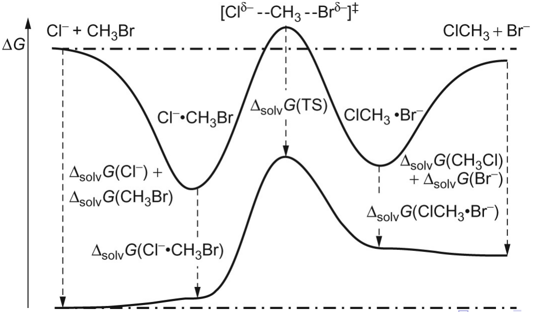
- Solvation energy from few (neutral solute) to hundreds of kcal/mol (ions) in water
- Inclusion of solvent effects may change the geometry, charge distribution and conformational preferences

Example: Reactivity of charged species

- S_N2 substitution

$$Cl^- + CH_3Br \rightarrow Br^- + CH_3Cl$$

- Kinetics
  - $k = 1.3 \times 10^{10}\ M^{-1}s^{-1}$ (gas phase)
  - $k = 3.3\ M^{-1}s^{-1}$ (acetone)
  - $k = 5.0 \times 10^{-6}\ M^{-1}s^{-1}$ (water)



Example: Reactivity of charged species

- DFT calculations (ωB97X-D functional, 6-31+G(d) basis set)
- SMD model for solvation (screening model based on density)

Species	$\Delta G_{(g)}$	$\Delta G_{(solution)}$
$Cl^- + CH_3Br$	0.0	0.0
$Cl^- \bullet CH_3Br$	–48.8	10.9
TS	13.3	100.7
$ClCH_3 \bullet Br^-$	–34.9	38.5
$ClCH_3 + Br^-$	–18.7	31.0

- Computed kinetics
  - $k = 2.85 \times 10^{10}$ M^{-1}s^{-1} (gas phase, 2.3 times larger than exp)
  - $k = 1.4 \times 10^{-5}$ M^{-1}s^{-1} (acetone, 2.4$\times$10^{-5} smaller)
- Inaccuracy due to approximations in SMD

Example: acid-base equilibria

- Dissociation of a weak acid HA in solvent (water)

$$\begin{aligned} \mathrm{HA} + \mathrm{H_2O} &\rightleftharpoons \mathrm{A^-} + \mathrm{H_3O^+} \\ K_A &= \frac{[\mathrm{H_3O^+}][\mathrm{A^-}]}{[\mathrm{HA}][\mathrm{H_2O}]} \end{aligned}$$

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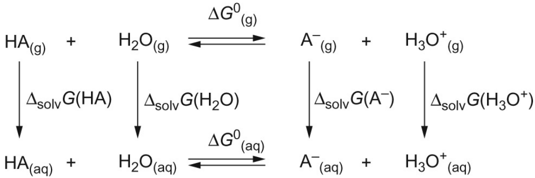
Thermodynamic cycle

$$\begin{aligned} \Delta G^0_{(aq)} &= \Delta G^0_{(g)} + \Delta G_{\mathrm{solv}}(\mathrm{A^-}) + \Delta G_{\mathrm{solv}}(\mathrm{H_3O^+}) \\ &- \{\Delta G_{\mathrm{solv}}(\mathrm{HA}) + \Delta G_{\mathrm{solv}}(\mathrm{H_2O})\} \\ \mathrm{p}K_A &= -\log_{10} K_A = \frac{-\Delta G^0_{(aq)}}{RT \ln 10} \end{aligned}$$



$$\begin{tikzcd}
\mathrm{HA}_{(g)} & + & \mathrm{H_2O}_{(g)} \arrow[r, shift left, "\Delta G^0_{(g)}"] \arrow[d, "\Delta_{\mathrm{solv}}G(\mathrm{H_2O})"] & \mathrm{A^-}_{(g)} \arrow[l, shift left] \arrow[d, "\Delta_{\mathrm{solv}}G(\mathrm{A^-})"] & + & \mathrm{H_3O^+}_{(g)} \arrow[d, "\Delta_{\mathrm{solv}}G(\mathrm{H_3O^+})"] \\
\mathrm{HA}_{(aq)} \arrow[from=u, "\Delta_{\mathrm{solv}}G(\mathrm{HA})"] & + & \mathrm{H_2O}_{(aq)} \arrow[r, shift left, "\Delta G^0_{(aq)}"] & \mathrm{A^-}_{(aq)} \arrow[l, shift left] & + & \mathrm{H_3O^+}_{(aq)}
\end{tikzcd}$$