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Introduction to ChemShell

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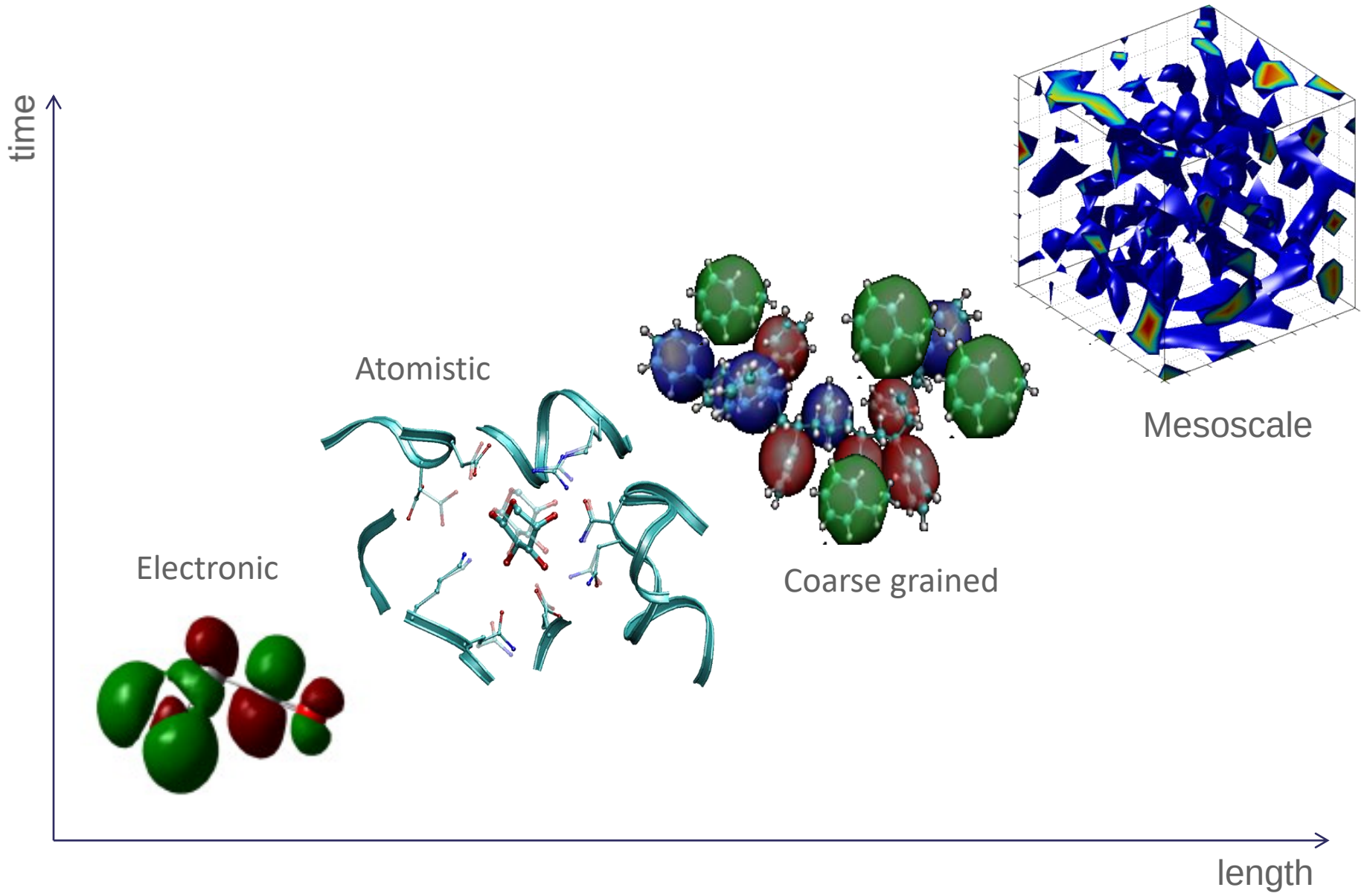
CCPBioSim Training Week 2021
1 October 2021



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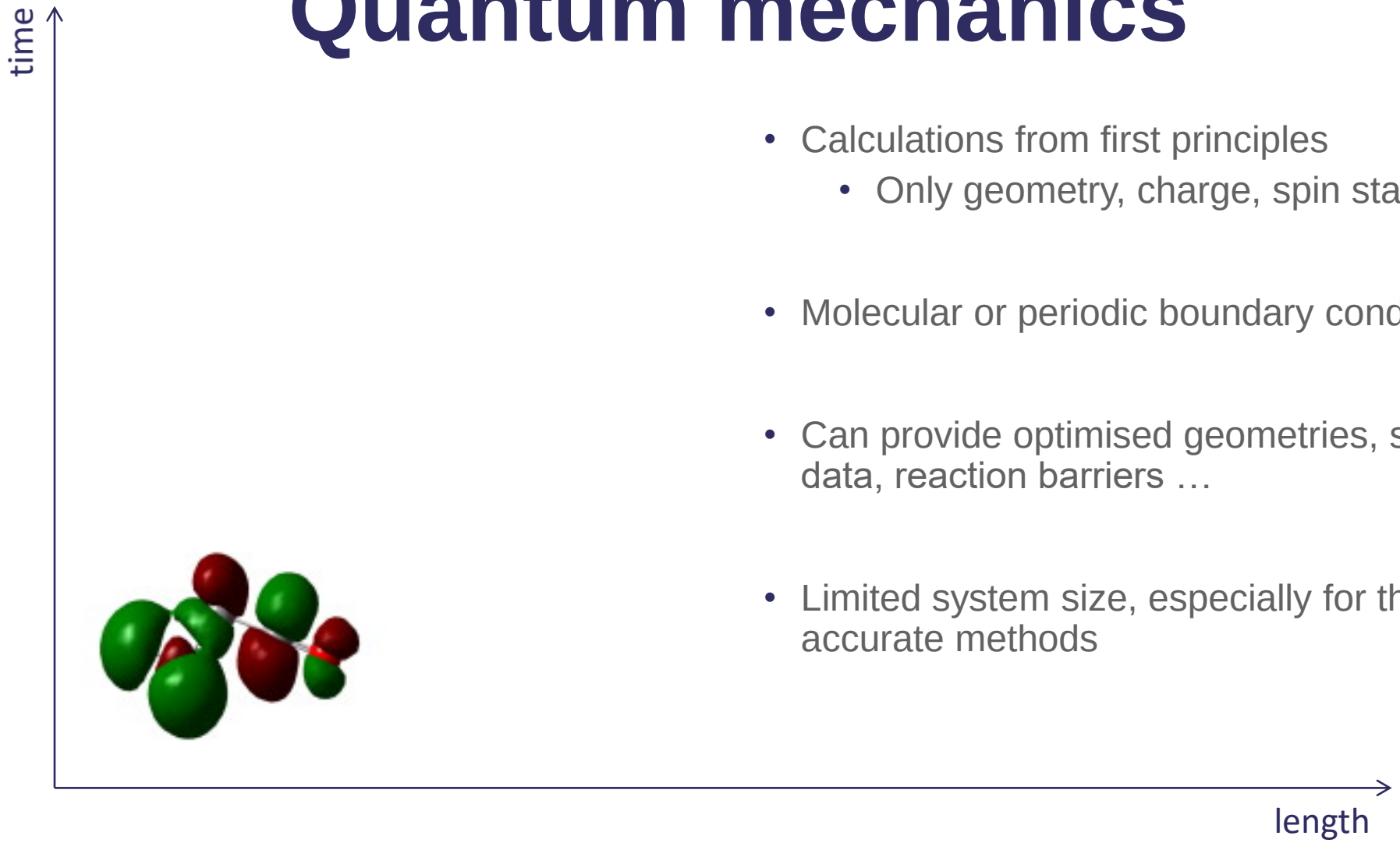
Quantum mechanics



- Calculations from first principles
  - Only geometry, charge, spin state required
- Molecular or periodic boundary conditions
- Can provide optimised geometries, spectroscopic data, reaction barriers …
- Limited system size, especially for the most accurate methods

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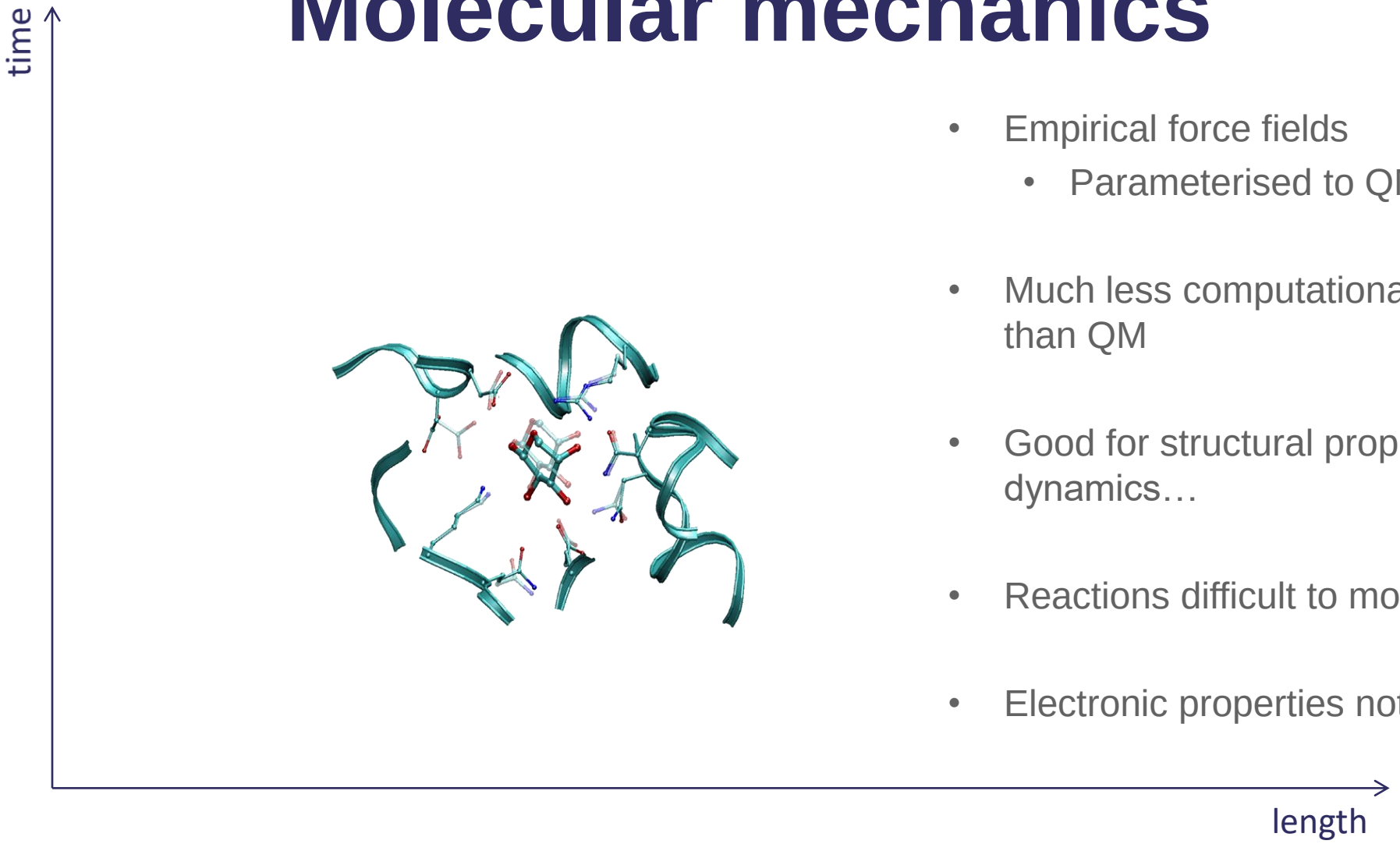
Molecular mechanics



- Empirical force fields
  - Parameterised to QM results
- Much less computationally demanding than QM
- Good for structural properties, dynamics…
- Reactions difficult to model
- Electronic properties not available

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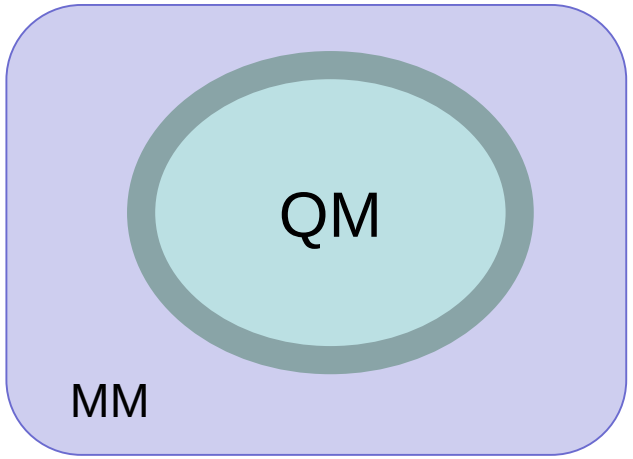
QM/MM methods

- **Overcome the QM size limit by combining quantum and classical approaches**
  - QM where an electronic description is required
  - MM for the environment





Nobel Prize for Chemistry 2013

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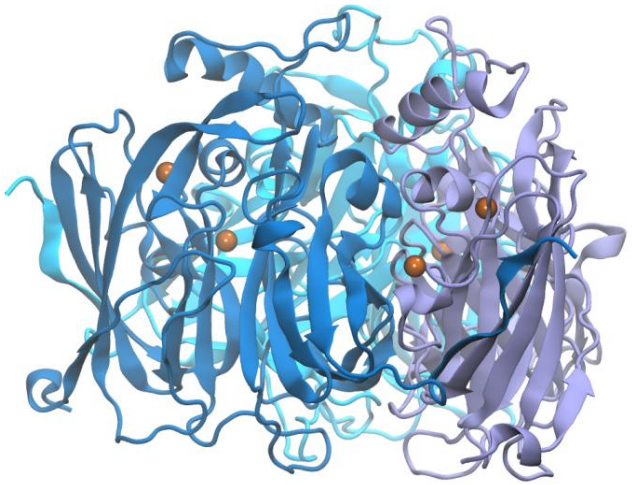
ChemShell QM/MM package

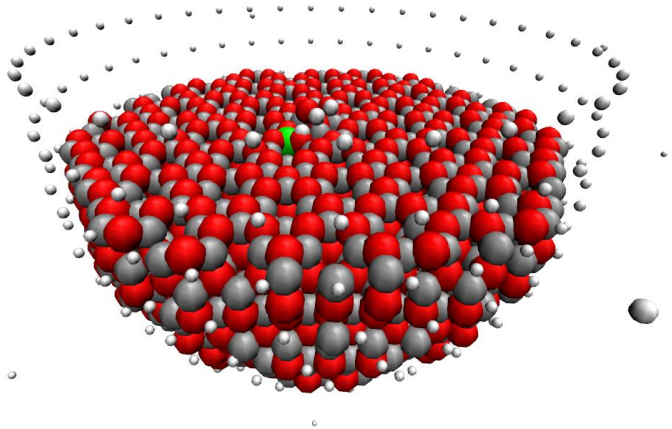
ChemShell

- Scriptable computational chemistry environment
- Flexible modular design
- Interfaces to a range of QM and MM codes

Biomolecular modelling



Materials chemistry



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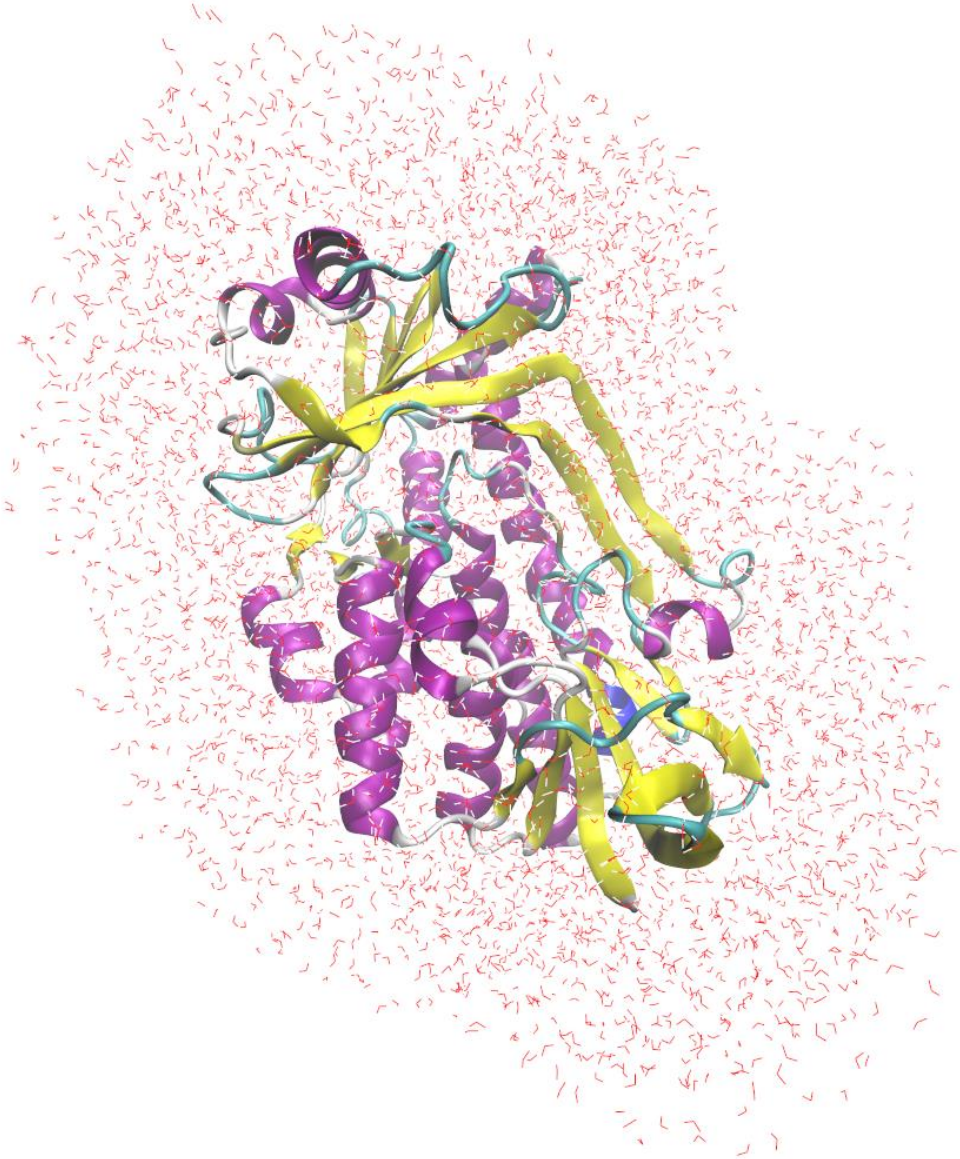
www.chemshell.org

Biomolecular modelling with ChemShell

- **Solvation shell around protein - not periodic**
  - Use molecular QM codes
- **Internal MM module**
  - Import standard force fields
- **QM region typically up to 300 atoms**



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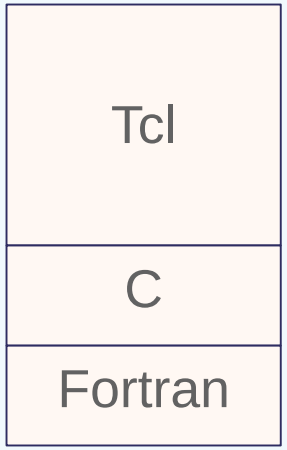
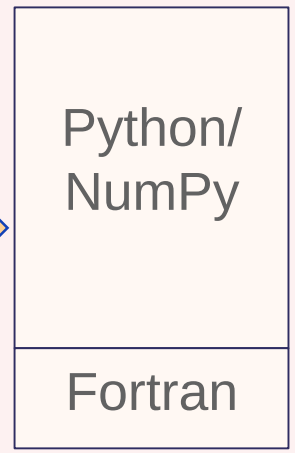
ChemShell versions

Tcl-ChemShell

- The original version (1990s onwards)
  - User interface controlled by Tcl scripts
- Proprietary licence (500 GBP for academic groups, free for UK-based groups)



Py-ChemShell



- EPSRC funded redevelopment (2014 onwards)
  - New embedding models
  - Complete rewrite of the codebase
  - New Python-based UI – easier for new users

open source™

- Reduce barriers to uptake, especially outside UK
- Encourage external developers

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JCTC 2019, 15, 1317

DOI: 10.1021/acs.jctc.8b01036

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JCTC Journal of Chemical Theory and Computation

Article

Cite This: J. Chem. Theory Comput. 2019, 15, 1317–1328

pubs.acs.org/JCTC

Open-Source, Python-Based Redevelopment of the ChemShell Multiscale QM/MM Environment

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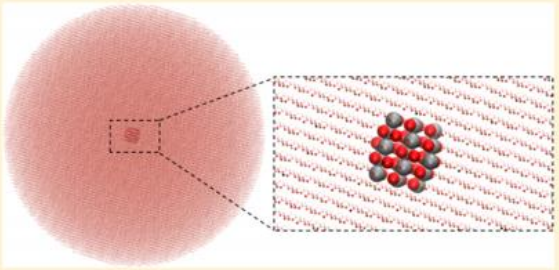
Supporting Information

ABSTRACT: ChemShell is a scriptable computational chemistry environment with an emphasis on multiscale simulation of complex systems using combined quantum mechanical and molecular mechanical (QM/MM) methods. Motivated by a scientific need to efficiently and accurately model chemical reactions on surfaces and within microporous solids on massively parallel computing systems, we present a major redevelopment of the ChemShell code, which provides a modern platform for advanced QM/MM embedding models. The new version of ChemShell has been re-engineered from the ground up with a new QM/MM driver module, an improved parallelization framework, new interfaces to high performance QM and MM programs, and a user interface written in the Python programming language. The redeveloped package is capable of performing QM/MM calculations on systems of significantly increased size, which we illustrate with benchmarks on zirconium dioxide nanoparticles of over 160000 atoms.



Using ChemShell

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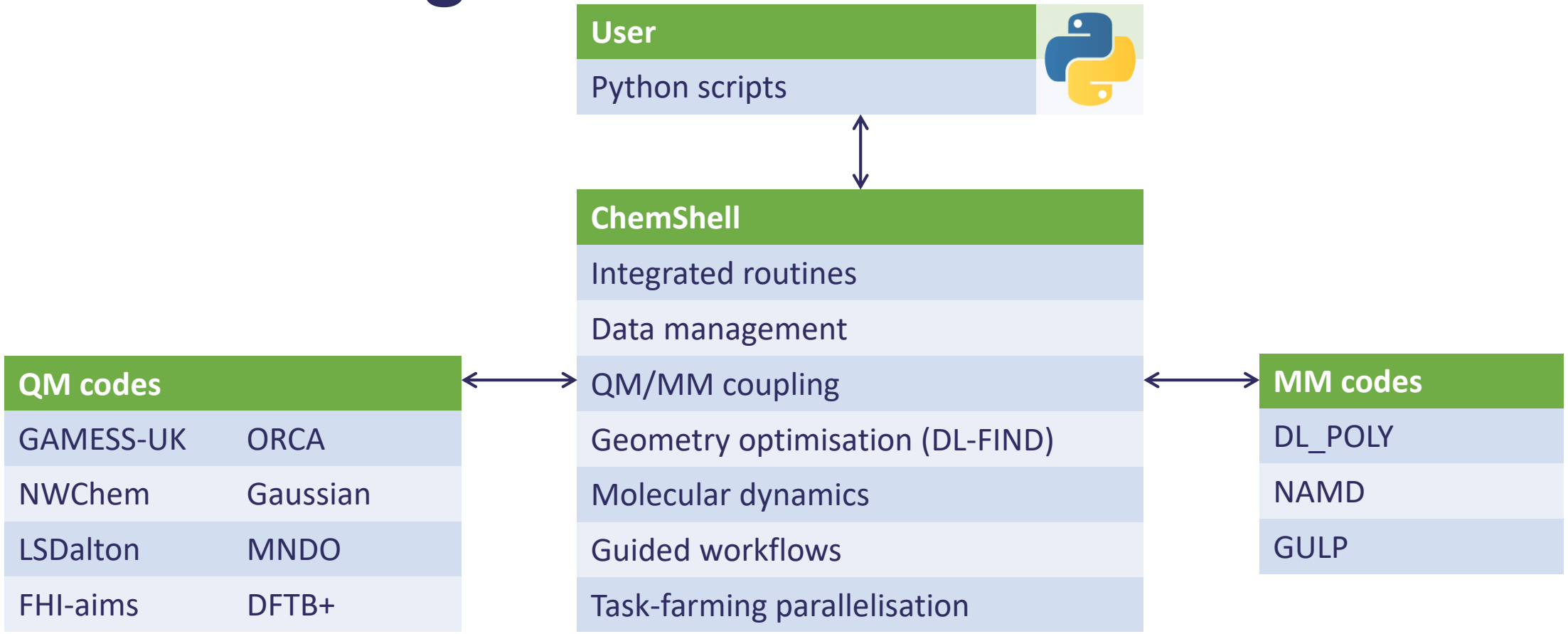
Modular design



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A simple (Py-)ChemShell script

```
from chemsh import *

water = Fragment(coords="water.xyz")

my_theory = NWChem(frag=water, method="hf", basis="3-21g")

my_calc = SP(theory=my_theory, gradients=True)

my_calc.run()

print("Energy = ", my_calc.result.energy)
```

Let's go over this line by line…

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Initialisation

```
from chemsh import *
```

- This line initialises ChemShell (chemsh) within the Python environment
- If you are unable to run ChemShell commands, it is probably because this line has been missed out

A simple (Py-)ChemShell script

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my_calc.run()

print("Energy = ", my_calc.result.energy)
```

ChemShell data storage

```
water = Fragment(coords="water.xyz")
```

- All data stored in ChemShell '**objects**' (Python classes)

- Object types include:
  - Fragment - molecular structure
    - Can create manually or from XYZ, PDB, JSON, etc.
    - Contains other objects with further info (point charges, shells, …)
    - Periodic systems supported (Cell object)
  - Result – contains results from a calculation (energy, gradients, Hessian matrix, …)
  - Field – data on a grid (e.g. for electrostatic potentials)

- Stored in memory unless explicitly saved (unlike Tcl-ChemShell)

A simple (Py-)ChemShell script

```
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my_calc = SP(theory=my_theory, gradients=True)

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print("Energy = ", my_calc.result.energy)
```

QM code interfaces

```
my_theory = NWChem(frag=water, method="hf", basis="3-21g")
```

- ChemShell '**theories**' are interfaces providing access to third party codes. QM interfaces include:
  - NWChem (PNNL, USA) is the main target for Py-ChemShell development
  - GAMESS-UK – developed at Daresbury
  - ORCA, good for biomolecules
  - DFTB+, fast semi-empirical DFT method

- `frag=water` – use the Fragment object defined in the previous line

- Option keywords are standardised as much as possible between interfaces:
  - `method='dft', functional='b3lyp'`
  - `charge=1, mult=2, scftype='uhf'`
  - `basis='6-31g'` (uses external code libraries)

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A simple (Py-)ChemShell script

```
from chemsh import *

water = Fragment(coords="water.xyz")

my_theory = NWChem(frag=water, method="hf", basis="3-21g")

my_calc = SP(theory=my_theory, gradients=True)

my_calc.run()

print("Energy = ", my_calc.result.energy)
```

Defining and running your calculation

```
my_calc = SP(theory=my_theory, gradients=True)
```

- SP (single point) is a ChemShell '**task**'
  - Defines the calculation that you want to perform (single point energy and gradient)
  - `my_theory` is the NWChem configuration defined on the previous line

```
my_calc.run()
```

- Execute the calculation defined above
- NWChem is now run either by a system call or as a directly-linked library

A simple (Py-)ChemShell script

```
from chemsh import *

water = Fragment(coords="water.xyz")

my_theory = NWChem(frag=water, method="hf", basis="3-21g")

my_calc = SP(theory=my_theory, gradients=True)

my_calc.run()

print("Energy = ", my_calc.result.energy)
```

Getting the result

```
print("Energy = ", my_calc.result.energy)
```

- The result object can be accessed as `my_calc.result`
  - `my_calc.result.energy` is a variable containing the energy

- Here, we simply print out the energy using Python's print command:

```
Energy = [-75.58528779]
```

A simple (Py-)ChemShell script

```
from chemsh import *

water = Fragment(coords="water.xyz")

my_theory = NWChem(frag=water, method="hf", basis="3-21g")

my_calc = SP(theory=my_theory, gradients=True)

my_calc.run()

print("Energy = ", my_calc.result.energy)
```

QM/MM calculations with ChemShell

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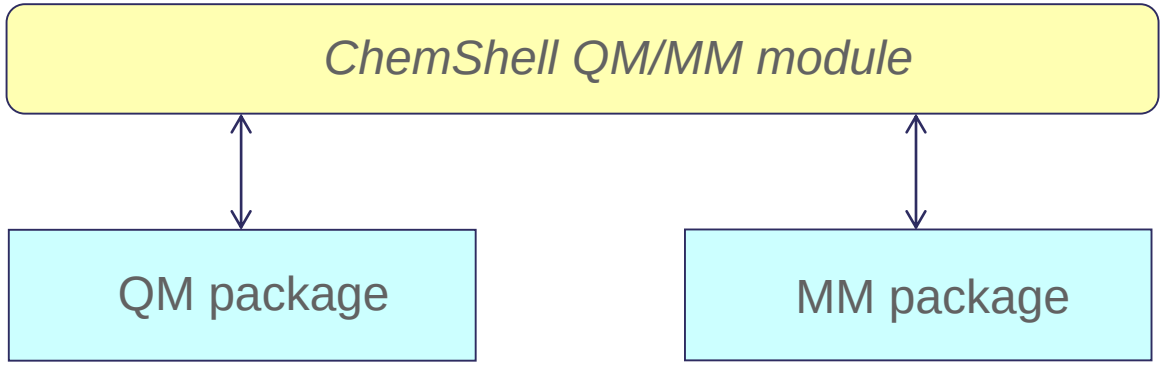
QM/MM calculations



- QM/MM calculations are controlled by the QMMM theory:

```
my_qmmm = QMMM(frag=butanol, qm_region=range(5),
               qm=NWChem(method="hf", basis="6-31g"),
               mm=GULP(ff=butanol.ff, molecule=True),
               embedding="electrostatic", coupling="covalent")

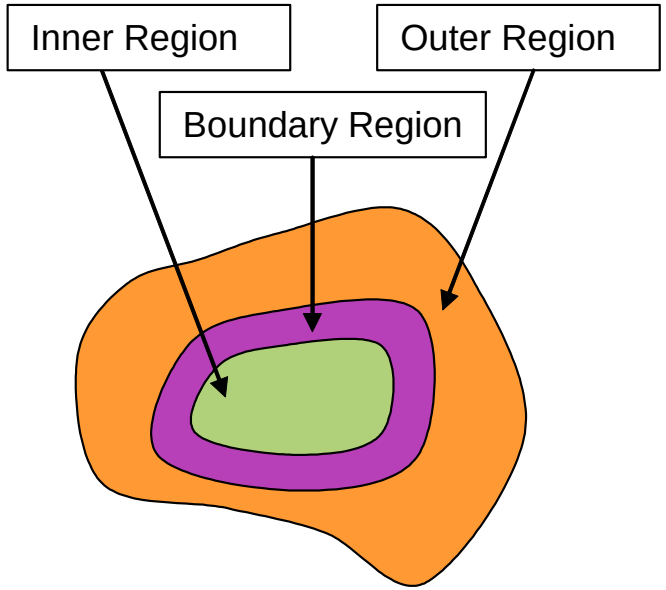
my_calc = SP(theory=my_qmmm, gradients=True)
```

Types of QM/MM

- **Additive scheme:** **E(MM, outer) + E(QM, inner) + E(QM/MM)**
  - No MM description of inner region required
  - Electrostatic coupling can be complex with link atoms
  - Can be applied to most systems e.g. solvation, enzymes, zeolites
  - Standard approach in ChemShell for biomolecules

- **Subtractive scheme:** **E(MM, full) + E(QM, inner) – E(MM, inner)**
  - Can treat polarisation of both regions at force field level
  - Full set of MM parameters required for inner region
  - Requires accurate forcefields to match potential energy surfaces
  - Eg: ONIOM method, Sauer QM-Pot (zeolites)

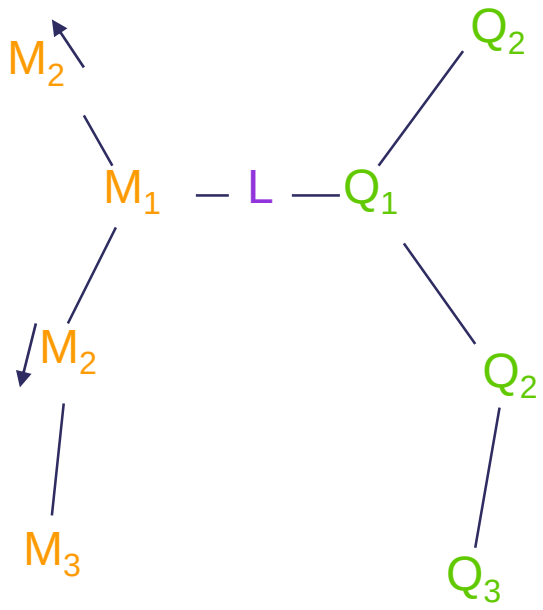
Termination of the QM region



- **Link atom scheme**
  - Terminating (link) atoms are invisible to MM calculations
    - Hydrogen, pseudo-halogen, etc.
  - For covalent systems, e.g. enzymes, zeolites
  - Choose bond to break carefully

- **Boundary region approaches**
  - Boundary atoms are present in both QM and MM calculations
  - Ionic systems: use pseudopotentials only on boundary atoms in QM calc

Link atoms charge shift boundary adjustment



- Some of the classical centres will lie close to link atom (L)
  - Artefacts can result if charge at the M_1 centre is included in Hamiltonian
- Adjustment:
  - Delete charge on M_1
  - Add an equal fraction of $q(M_1)$ to all atoms M_2
  - Add correcting dipole to M_2 sites (implemented as a pair of charges)
  - charge and dipole of classical system preserved
- Requested using `coupling='covalent'`

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Levels of QM/MM embedding

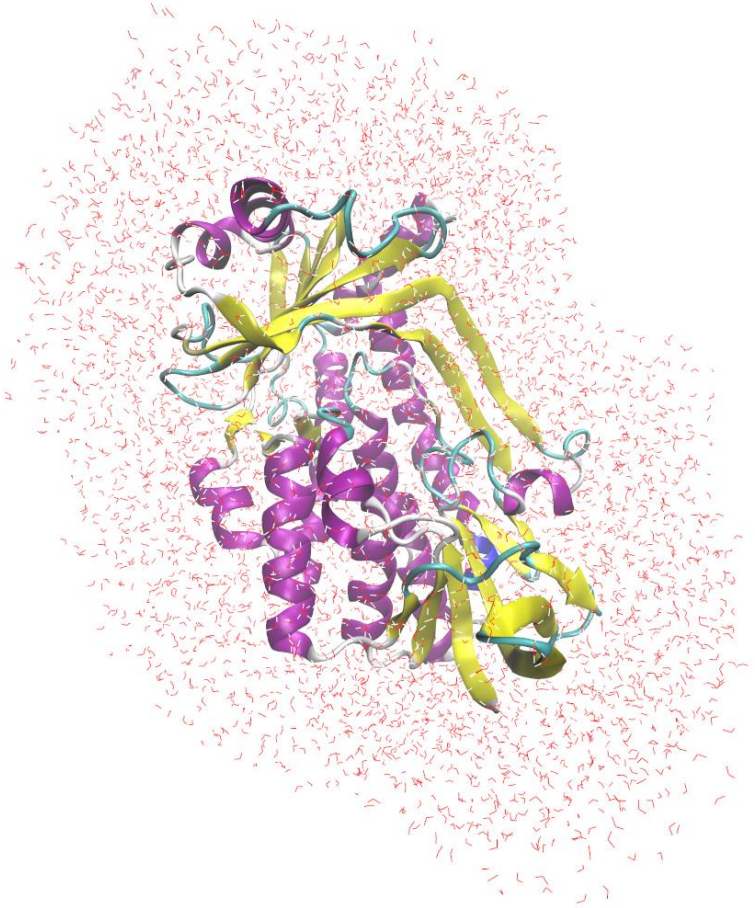
- **Mechanical embedding**
  - *in vacuo* QM calculation coupled classically to MM via point charges at QM nuclear sites
  - Straightforward, separable QM and MM calculations
  - No model for polarisation of QM region

- **Electrostatic embedding**
  - MM atoms appear as centres generating electrostatic contribution to QM Hamiltonian
  - QM calculation polarised, MM environment not polarised

- **Polarised (MM) embedding**
  - Shell model potential used in ChemShell
  - Mutual polarisation – iterated to self-consistency
  - Important for ionic systems, e.g. metal oxides

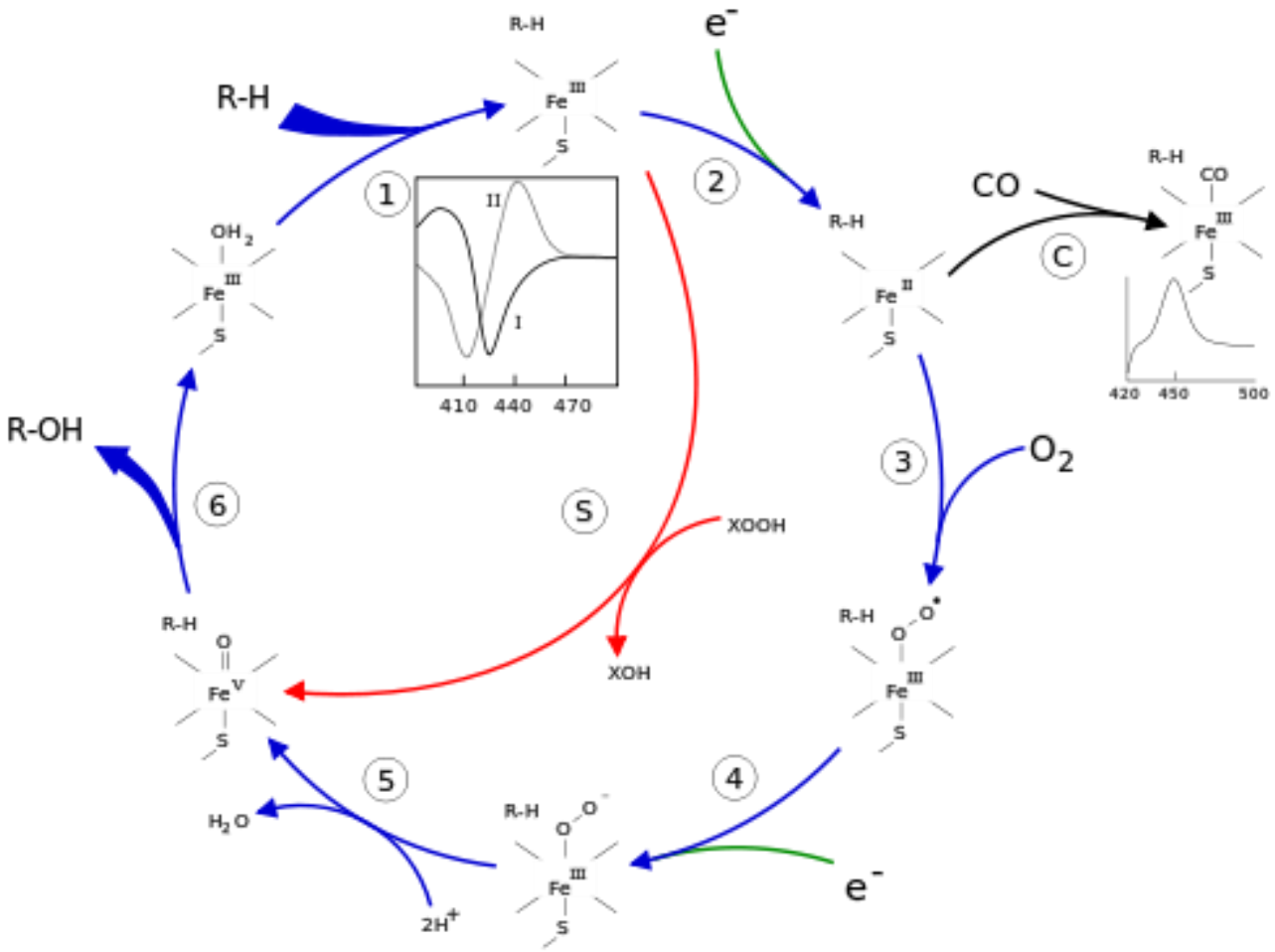
Common choices for biomolecules

- DL_POLY MM module
  - Import CHARMM or AMBER force field
- Wide variety of QM codes used
  - Almost all support electrostatic embedding
- Usual QM/MM approach:
  - Additive method
  - Electrostatic embedding
  - Link atom scheme to handle boundary



Example: cytochrome P450 family

- Extensively studied with QM/MM by a number of groups
- QM/MM used to identify species in catalytic cycle and understand their chemical properties
- Key intermediate Cpd I predicted by QM/MM before discovery



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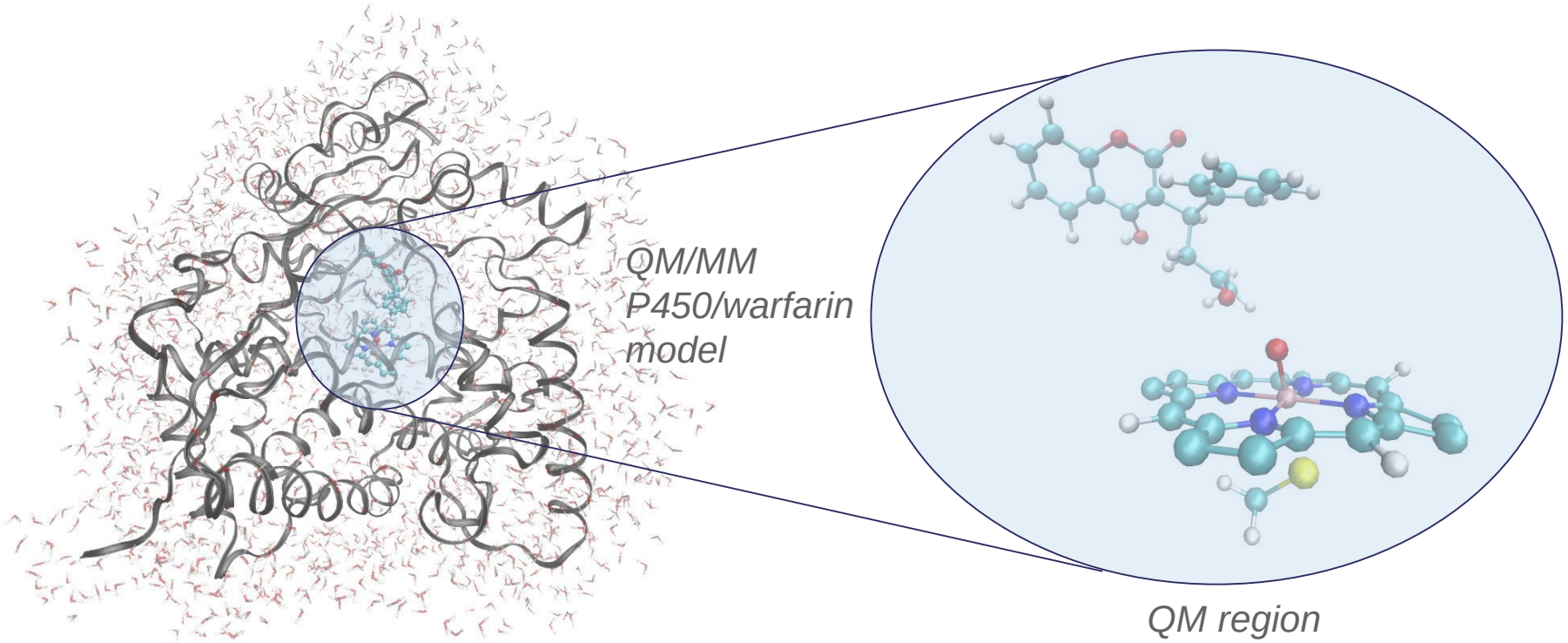
ChemShell biomolecular modelling workflow

- Solvated and equilibrated using NAMD (see later talks)

- Take a series of “snapshots” (sampled structures from MD run)
  - Minimise using QM/MM (QM = DFT)
  - Further QM/MM optimisations to find barriers, reaction paths, …



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Geometry optimisation with DL-FIND

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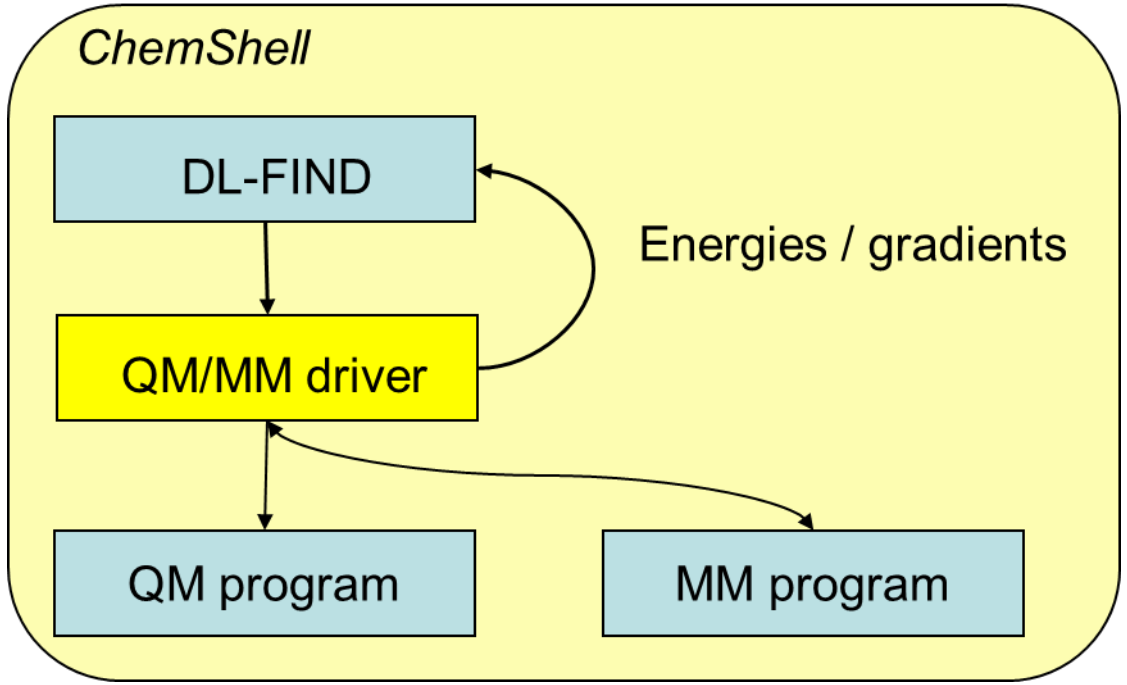
DL-FIND

- Open-source geometry optimisation library
- Interface to ChemShell for QM/MM optimisations



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J. Kästner, J.M. Carr, T.W. Keal, W. Thiel, A. Wander, P. Sherwood, *J. Phys. Chem. A,* 2009, **113**, 11856

A simple minimisation example

```
from chemsh import *

water = Fragment(coords="water.xyz")

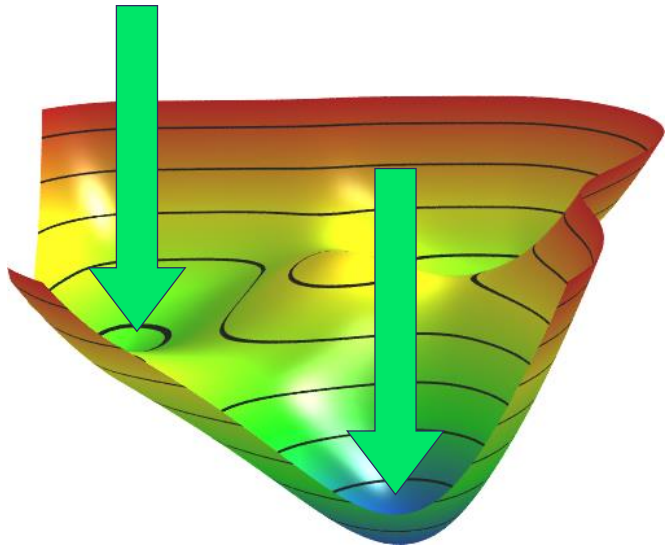
my_theory = NWChem(frag=water, method="hf", basis="3-21g")

my_calc = Opt(theory=my_theory)

my_calc.run()
```

- `Opt` is the ChemShell task that calls a DL-FIND optimisation
- Otherwise **identical** to the `SP` example
- Default settings used (Cartesian coordinates, 100 cycles maximum, default convergence)

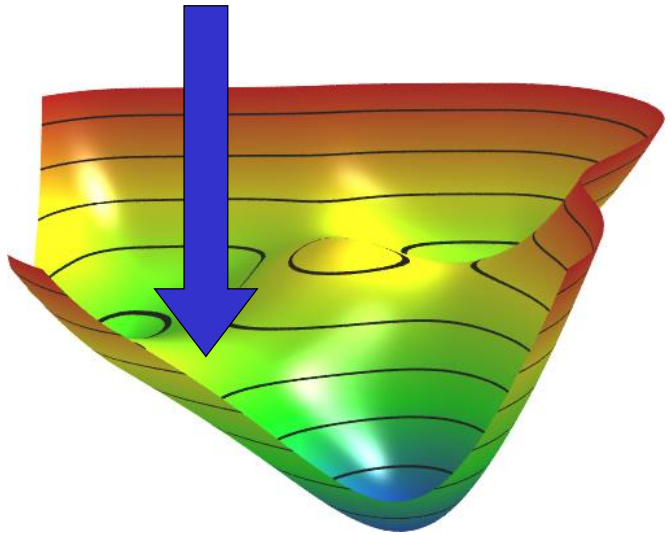
Local minimization algorithms



```
algorithm="sd"/"cg"/"nr"/"lbfgs"/"dyn"
```

- Steepest descent
- Conjugate gradient
- Newton-Raphson/quasi-Newton
  - Choice of initial Hessian approximation and update scheme
- Damped molecular dynamics
- L-BFGS (default)
  - Limited-memory variant of the BFGS quasi-Newton method
  - Full Hessian not stored, uses last *M* steps for updates
  - Suitable for large systems

Transition state optimization



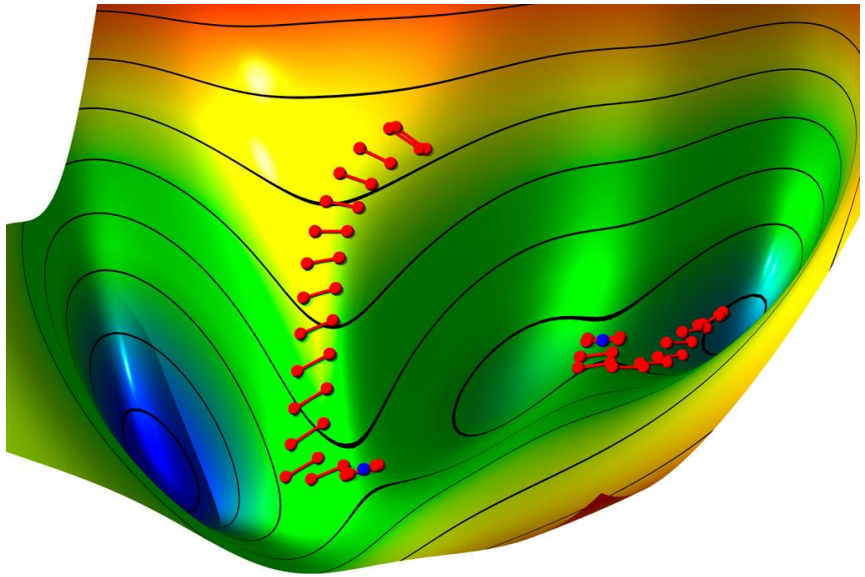
```
algorithm="prfo"
```

- Partitioned rational function optimisation (P-RFO)
  - Maximises in direction corresponding to negative eigenvalue in Hessian, minimises in all other directions.
- Requires a Hessian calculation – only suitable for small systems
- Consider more efficient alternatives!

Dimer method

```
dimer=True
```

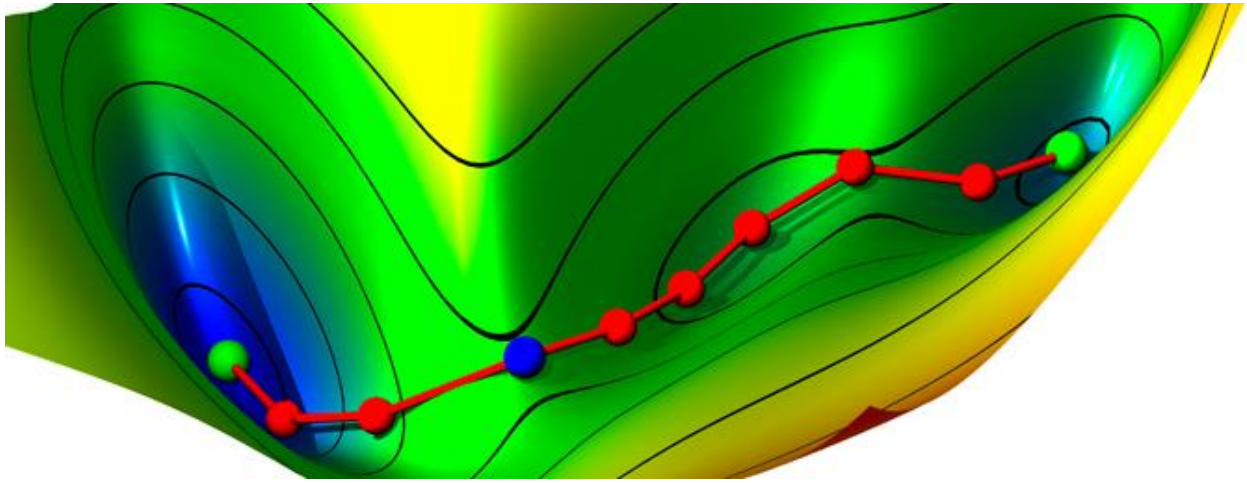
- Dimer: two images of the system, constant distance apart
- Rotation: difference of the forces
  - Aligns dimer with Hessian mode with lowest eigenvalue
- Movement:
  - In dimer direction: maximise
  - Perpendicular to dimer direction: minimise
- Converges to first-order saddle points
- **No Hessian required** so suitable for large systems



Nudged elastic band

```
neb="frozen"/"perpendicular"/"free"
```

- Multiple images, connected by spring forces
  - Specify multiple input fragments using **`coords2=`**
- Converges to the minimum energy path between endpoints
- Climbing image to find transition state
- Usually optimise endpoints first ('frozen' NEB)



- Two stage strategy:
  1. Find a loosely converged transition state with NEB
  2. Converge with dimer method

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Get the code at

www.chemshell.org

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