ESS/ILL User Meeting

BigDFT

New on-line DFT approach to analyse neutron diffraction crystallography and SANS data

Viviana Cristiglio, Luigi Genovese

Institut Laue Langevin, Laboratoire de Simulation Atomistique - L_Sim

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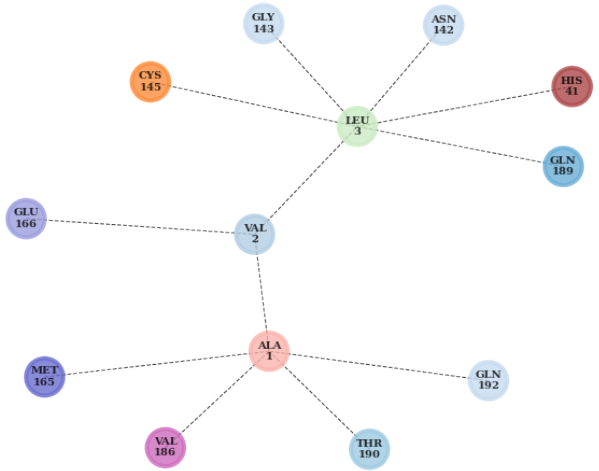
Grenoble

Complexity of biological systems

Various conditions

- Large systems of many thousand atoms
- Atomistic models should model atomic interactions, yet electronic information may be important
- Difficult to obtain predictivity without arbitrariness

✘ A number of important implications



What we will illustrate today

Quantum Mechanics (DFT) may be needed

- Whenever DFT is necessary to study the electronic structure of the systems, it is important to provide the tools to *interpret* experimental data
- Need of new tools developed especially for the study of biological systems

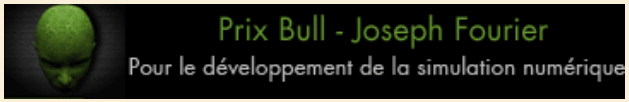
☞ The BigDFT code provide a new paradigm of analysis

Main ingredients

- PDB files from neutron crystallography, Cryo-TEM, MD simulations, ...
- Remotely accessible (super) computing platform
- A post-processing infrastructure easy-to-use

BigDFT: DFT with wavelets

A DFT code conceived for HPC (`www.bigdft.org`)

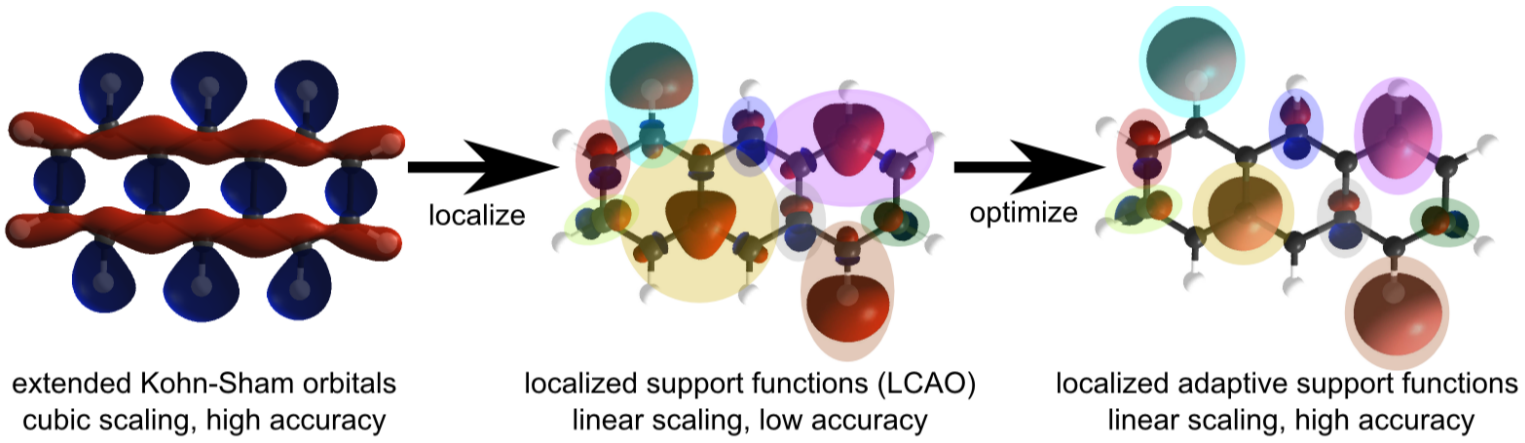
- DFT calculations up to many thousands atoms
- 👉 An award-winning HPC code 

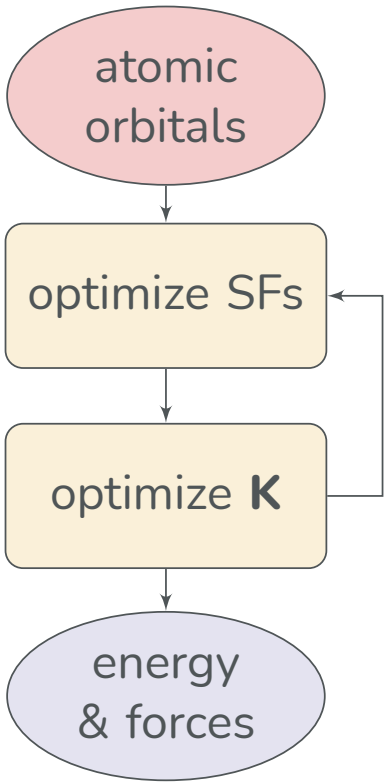
- BigDFT has been conceived for massively parallel etherogeneous architectures since more than 10 years (MPI + OpenMP + GPU)

Code able to run routinely on different architectures

- GPU accelerators since the advent of double-precision GPGPU (2009)
- Various large calculation projects since 10 years
- ✔ A code conceived for supercomputers

A Linear Scaling Algorithm





Accurate Minimal Basis

- Employs optimized DoF to express accurately and efficiently the DFT solution
- Able to treat systems up to tens of thousand atoms
- Ideal framework to reduce the complexity of the description

How DFT should be used at this scale?

In practice:

- O(N) codes have been able to compute large systems for many years now.
- And yet, how often do you encounter research being done with DFT involving systems of many tens of thousands of atoms?

Issues related to DFT in large systems

- Enthalpy challenge: are DFT functionals really more accurate than a well tuned forcefield?
- Entropy challenge: can DFT capture the full set of conformations of a large system?

The key added-value of DFT is not accuracy, but insight

Complexity Reduction: QM Fragments

- Consider a system of interest, which we have arbitrarily partitioned in to two sets of atoms. We can call these sets QM Fragments.
- We introduce the concept of *Complexity Reduction* - dividing large, complex systems into chemically meaningful fragments and measuring their interaction.

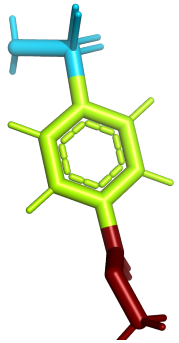
Robust and well-defined indicators

- Purity Indicator - similar to the classical concept of Atomic Valence.
- Fragment Bond Order - similar to standard atomic bond order.

Automatic Fragmentation of Systems

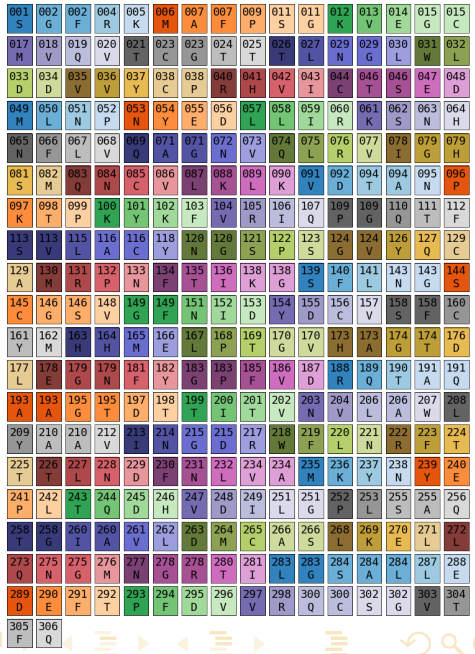
Small Molecules - From Atoms Up

- Automatic: We can re-organize a system into fragments without prior knowledge.
- Robust: Non-expert DFT users can interpret the information coming out of DFT calculations.



Large Biomolecules

- Proteins are often already divided into fragments based on their Amino Acids.
- Yet not all amino acids are equally good fragments. We can combine them together to build a more coherent picture.



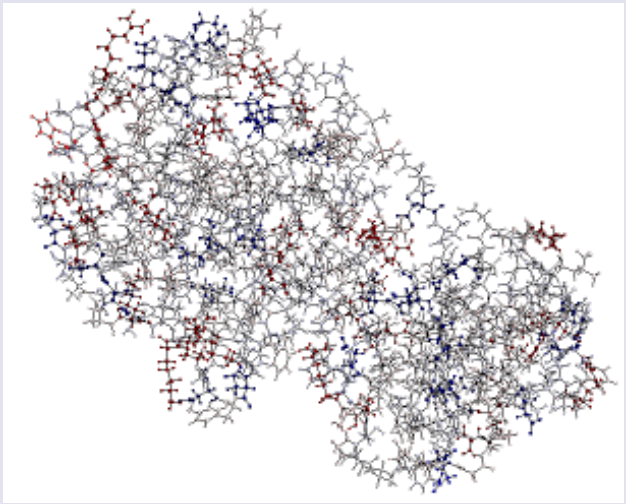
How this is related to Neutrons?

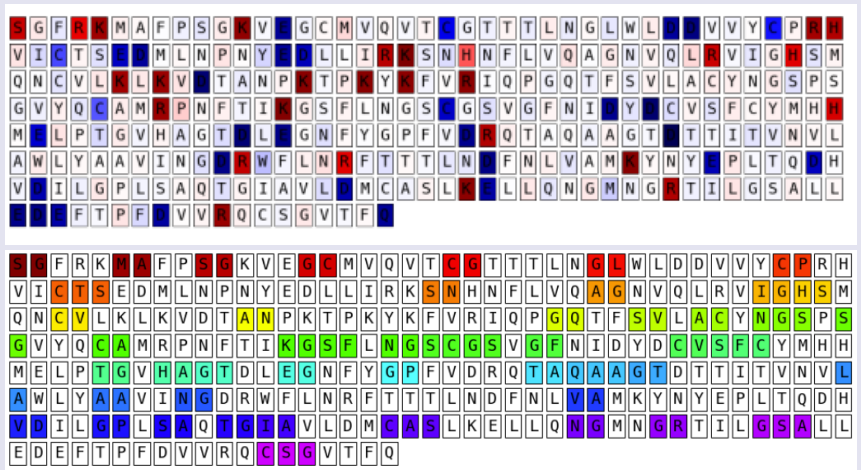
From Neutron crystallography to DFT

- Direct process of PDB
- ✎ Neutron Crystallography files contain also the positions of the deuterium → protonation state is given

Amino acid charges of SARS-CoV-2 MPro

(PDB 7JUN - Oak Ridge)





Workflow ready to be extended

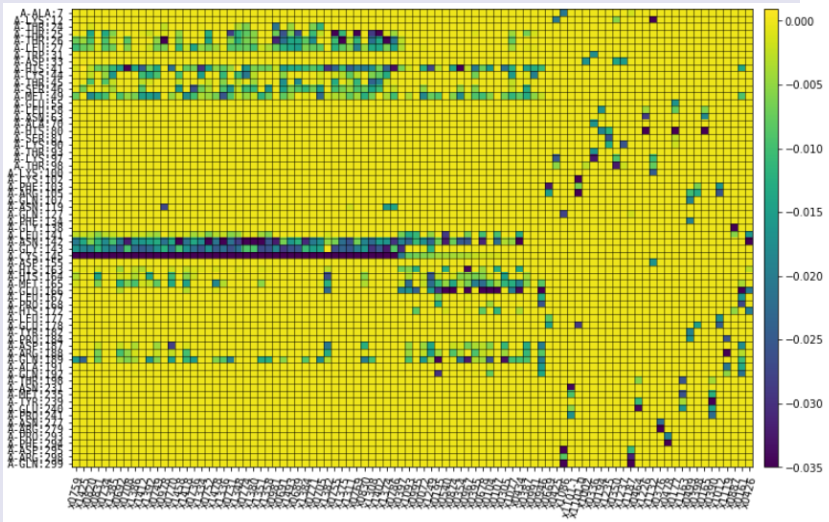
Other QM observables can be analyzed

- Interaction maps can be represented (eg. role of the crystallographic solvent)
- High throughput analysis can be performed on NC databases

COVID XChem fragments project

MPro crystal structures of 92 different small inhibitors

☛ Map the interactions of inhibitors with enzyme



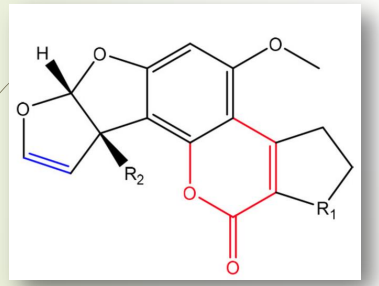
Enzymatic Activity of Laccase

Case Study

Laccase is a potential bioremediator for Aflatoxin contamination

AFLATOXIN B1 (AFB1)

- PRODUCERS: Genus *Aspergillus*
- STRUCTURAL TRAITS: Difuranocoumarin derivatives produced by a polyketide pathway.



R_1 = C=O, -(C=O)-O- or C-OH

R_2 = H or OH

Aflatoxicosis:
Chronic: Liver cancer, Immunosuppression, Death.
Acute: Death.

- TOXICITY:
  The most carcinogenic metabolite in nature. The lactone ring is the main responsible for toxicity, and secondarily the terminal double bond of the difuran moiety.
  Cytochrome P450 activates AFB1 into a highly reactive epoxide that **easily binds to DNA and proteins**, inducing mutagenicity and cytotoxicity.

Combination of DFT and Structural caracterization

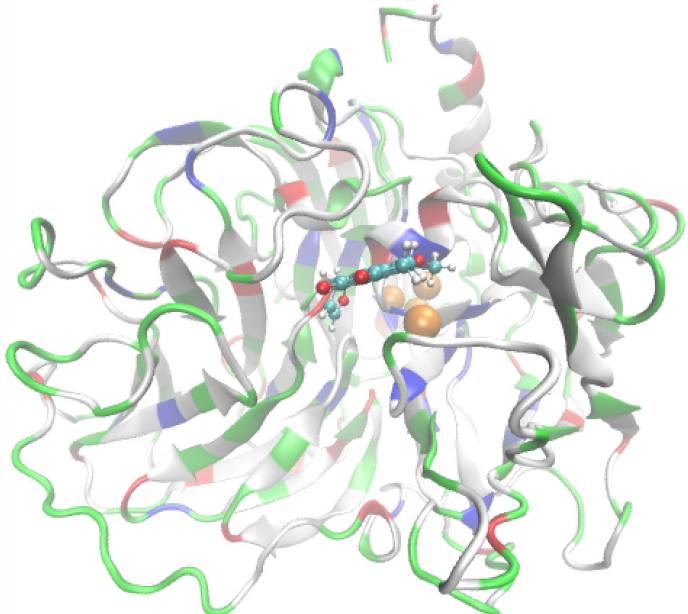
Structural analysis informed by SANS

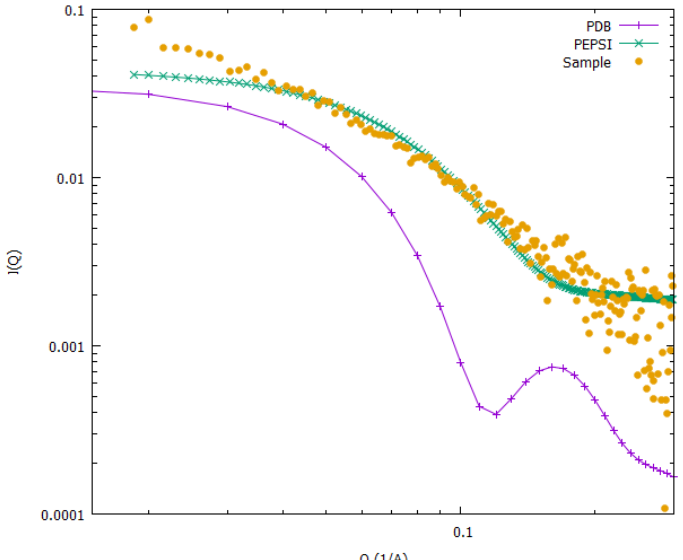
Aflatoxin Degraded by Laccase Enzyme

Open Questions and present projects

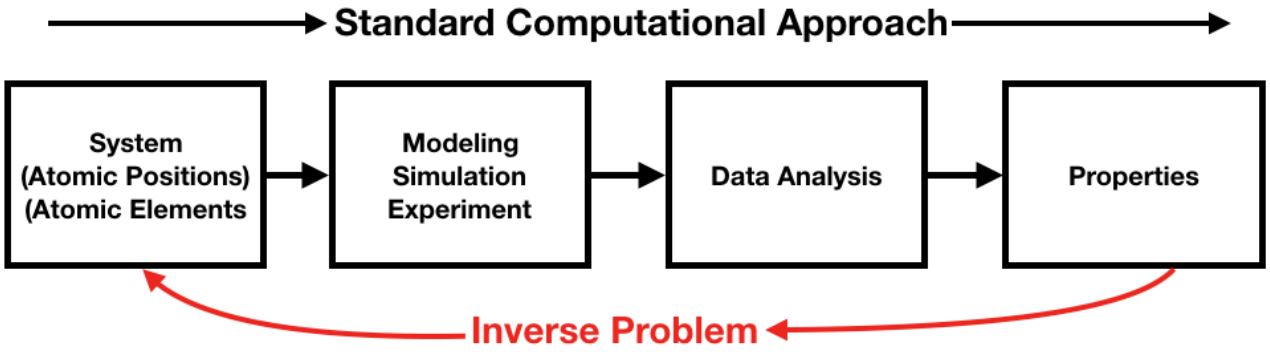
- How can we break down this enzyme into smaller parts, and which of those parts are relevant for the reaction?
- What interplay between toxin and environment?
- Why are some toxins easier to degrade than others?

☛ SANS data can be used to validate DFT structures





Going from Understanding to Design



The Inverse Problem of Computational Science

- Mechanistic models might be used to gain detailed insight into individual systems.
- However, the goal of bioremediation is not understanding, but design.
- Inverse problem: given a set of desirable properties, how to we build a system that produces those properties?

Towards a new scientific paradigm

- Systems of interest in biology may *start* to be modelled
- Structural information coming eg. from Small-Angle Scattering might be put in relation to such investigations

Implications

Development of a method capable of informing biological problems without arbitrariness (e.g. antibiotic resistance, antibodies and drug development etc.)

- First steps towards a rational, iterative amelioration of laccase focused on substrate specificity.

Quantum-as-a-Service approach

A dedicated VISA platform is under implementation
Collaboration L_Sim (CEA Grenoble) and CS Group (ILL)

PyBigDFT

Pre- and Post-processing of simulations are performed via a `Python` module

HPC

Calculations triggered remotely on a super-computer from a Jupyter notebook (AiiDA framework)

Userclub

Simulation can be processed from a platform next to experimental data (ILL User Club access)

Database

Large databases of biological systems can be created

New insights for (neutron) data analysis

- Dedicated routine for neutron crystallography data interpretation
- Possible improvement from SANS data

In a nutshell

Summary

- DFT shouldn't be employed for large systems just on the hope of accuracy, but instead with the goal of insight.
- Complexity Reduction - We have developed a way to use information from DFT to generate coarse-grained views of a system by defining reliable fragments and measuring their interaction.

Packaging

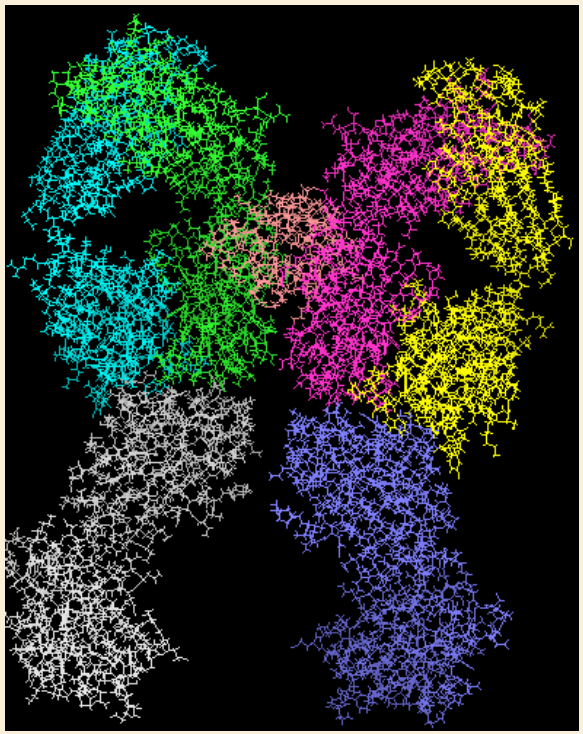
- The complexity reduction framework presented here is available through our PyBigDFT package.
- Postprocessing can be done even for large systems on a typical workstation.
- This combination create interesting opportunities for interdisciplinar collaborations

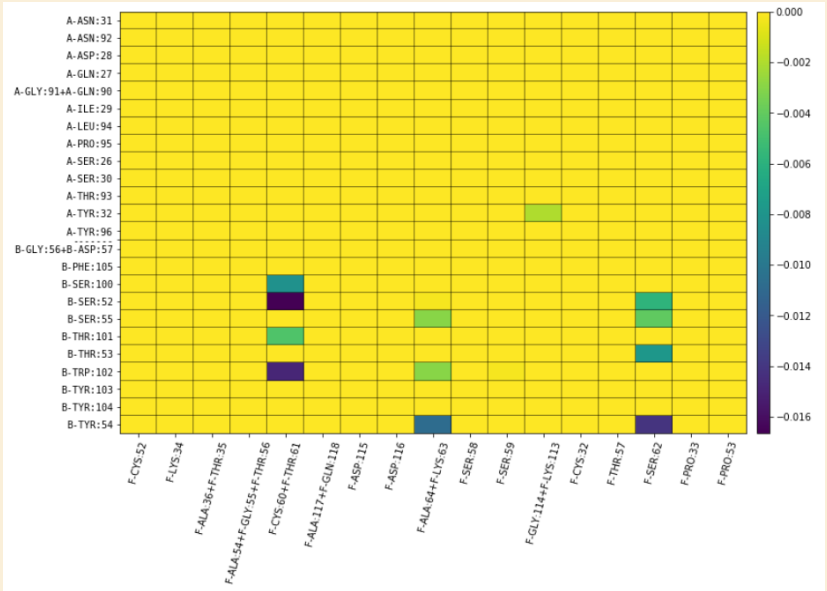
Lots of Systems of interest in Biology

Large systems are routinely accessible

Linear Scaling code → CPU time *per atom*
Example: 1400 Residues (One Monoclonal Antibody). 3h of walltime on 32 nodes of IRENE-Rome Machine

Reduce the interactors in a biological system





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Rome M. D'Alessandro

Catania G. Fisicaro

Advantage of aiida technology

We have implemented the "traditional" flavour of AiiDA plugin. `pip install aiida-bigdft`

▸ BigDFT plugin

Integrated in PyBigDFT

▸ PyBigDFT AiiDA runs

A technology that makes the notebook a *console* to launch the job and to analyze production data

`AiidaCalculator` ☛ used to remotely submit the job

```
from BigDFT import AiidaCalculator as A
study=A.AiidaCalculator(code="bigdft@localhost",
         num_machines=1,mpiprocs_per_machine=1,
         omp=1,walltime=3600)
%load_ext jupyternotify
%notify
hgrid_cv.wait()
>>> '0 processes still running'
```

Employed for (Virtual?) Benchmarks, Production.

Future scientific directions

Linear-Scaling DFT calculations based on wavelets

- Robust convergence, high accuracy and flexibility
- Reduction in degrees of freedom $\rightarrow$ large systems
- Different level of descriptions (controlling the precision) QM $\supset$ Fragments $\supset$ Atomic charges
- Opens up new possibilities

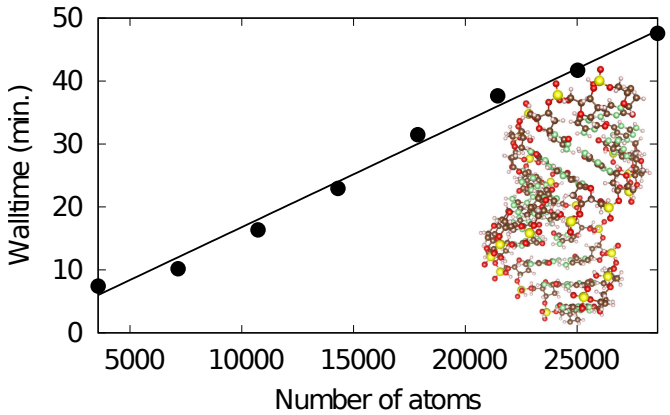
Challenges and future directions

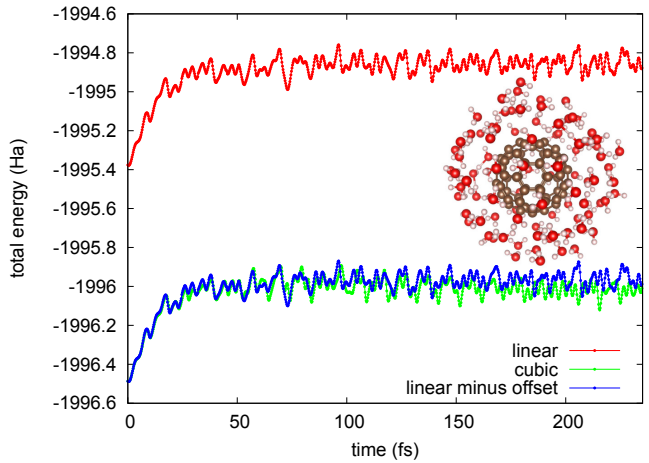
- Explore interplay environment $\leftrightarrow$ electronic excitations (CDFT, QM/MM, statistics...)
- Provide high quality back end for different communities (Biology, Electro-Chemistry, ...)

Accurate DFT for 1000s of atoms

Linear Scaling DFT with Wavelets

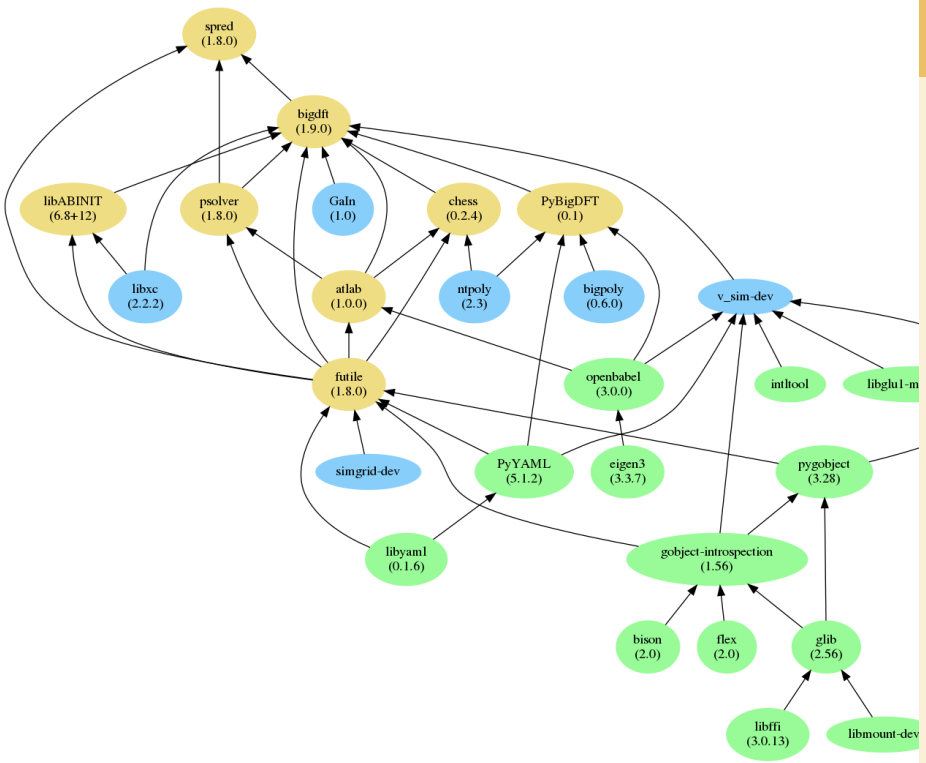
- minimal, localized basis with wavelet accuracy – can treat $> 10,000$ atoms
- applicable to a range of materials, including metals
- accurate forces – geometry optimizations, molecular dynamics





LS-BigDFT References: { Mohr, Ratcliff Boulanger, LG *et al.*, J. Chem. Phys. **140**, 204110 (2014)
Mohr, Ratcliff, LG *et al.*, Phys. Chem. Chem. Phys. **17**, 31360 (2015)
LS-BigDFT Metals: Mohr, Eixarch, Amsler *et al.*, J. Nucl. Mater. Energy **15**, 64 (2018)
CheSS: Mohr, Dawson, Wagner *et al.*, J. Chem. Theory Comput. **13**, 4684 (2017)

Code release and distribution



Modularity first

BigDFT-suite is a collection of different independent libraries with own build system. Enables to include third-party libraries (green) and upstream modules (blue)
☛ Dependencies can be expressed easily in the jhbuild-based bundler.

Containered `hub.docker.com/r/bigdft`

BigDFT suite is relased as a `docker` container (GPU-direct ready) ☛(also on NVidia NGC repository)
Different Flavour of containers: Runtime, SDK, Console