High-Performance Computing in Pharmaceutical Research:

From Virtual Screening to All-Atom Simulations of Biomolecules

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Outline

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- Why HPC in Pharmaceutical Research ?
- Application Examples:
  - Virtual screening
  - High-level quantum mechanical calculations
  - Molecular dynamics simulations of proteins
  - In-silico profiling of molecules
- Summary
- Future Perspective

The Drug Discovery Process: Pharmaceutical Research

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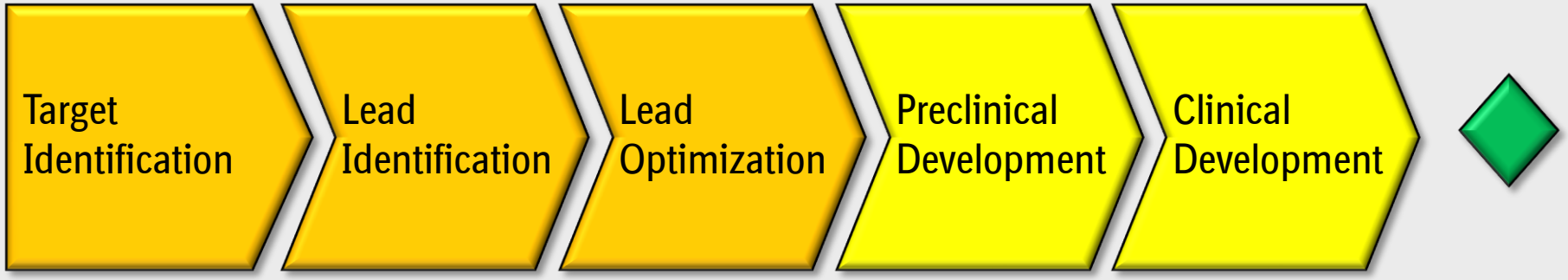

High Performance Computing in Pharmaceutical Research:
Support the identification and optimization of new molecular entities by computational methods.

The Drug Discovery Process: Pharmaceutical Research

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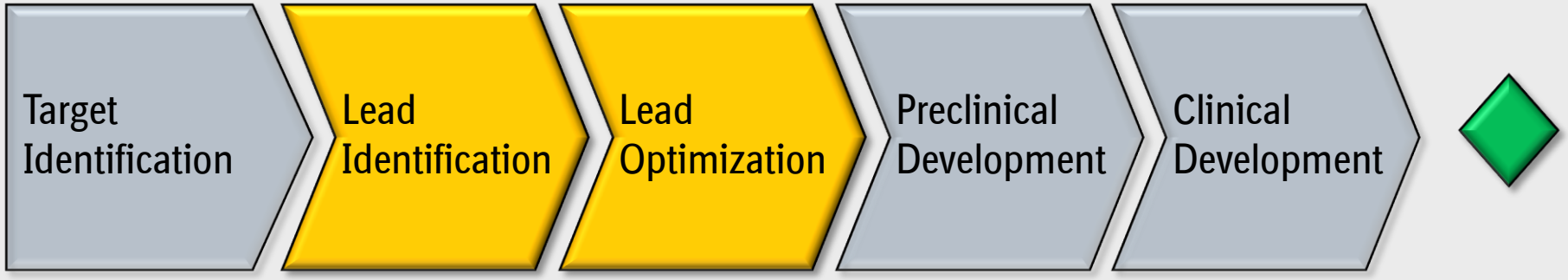

High Performance Computing in Pharmaceutical Research:
Support the identification and optimization of new molecular entities by computational methods.

Virtual Screening
Find the needle in the haystack !

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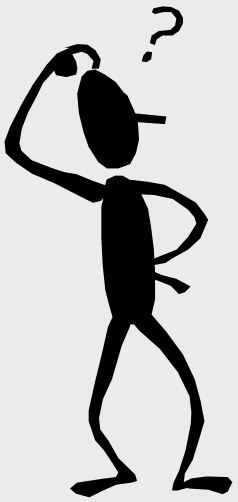
Which of these molecules could be biologically active?



Trillions of compounds

10^{12}

10^{2}-10^{3}

N.B. Some estimates tell us that the chemical universe comprises more than 10^{50} molecules !

Virtual Screening

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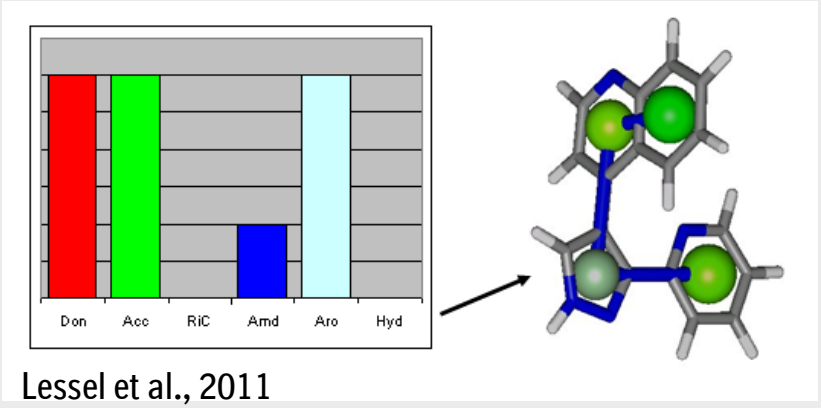
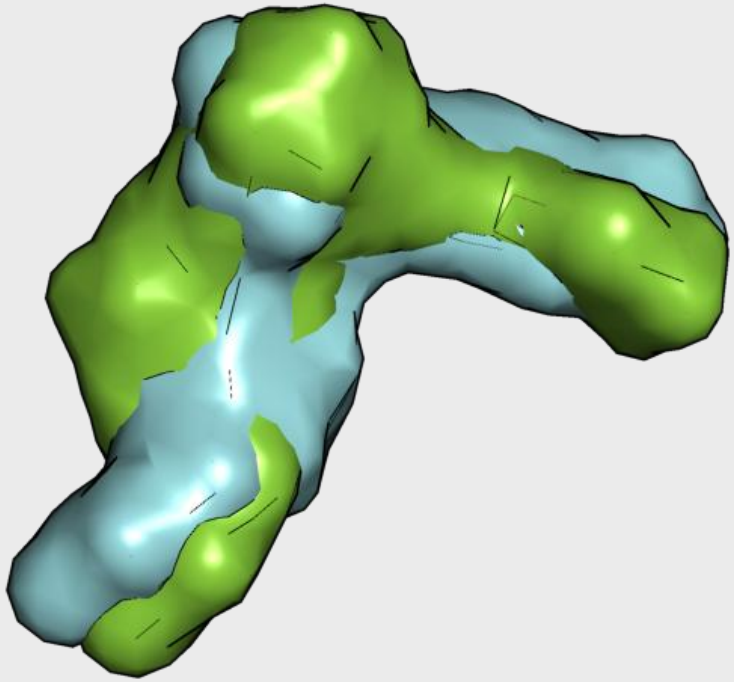
You already know that a certain molecule binds to your protein of interest.

⇨

Look for other (similar ?) molecules that might also bind but display different overall properties.



Lessel et al., 2011



Comparison of descriptors, bit strings, cliques, ...

... or 3D shapes.

Virtual Screening

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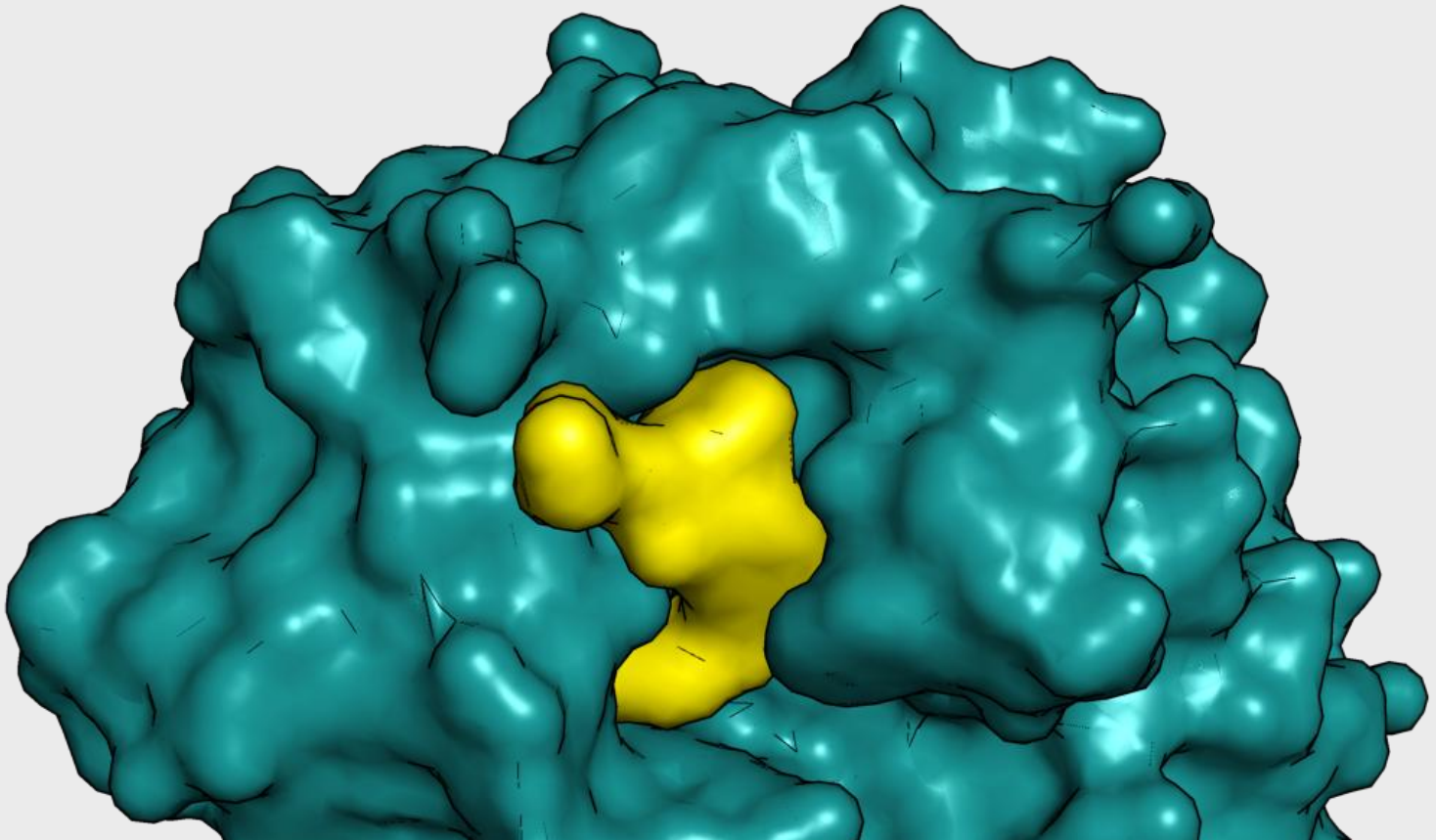
You know the 3D structure of your protein of interest and you know where the molecule should bind.

⇨ Look for molecules that might fit into the binding pocket



Thrombin with bound ligand

High-level Quantum Mechanics Calculations

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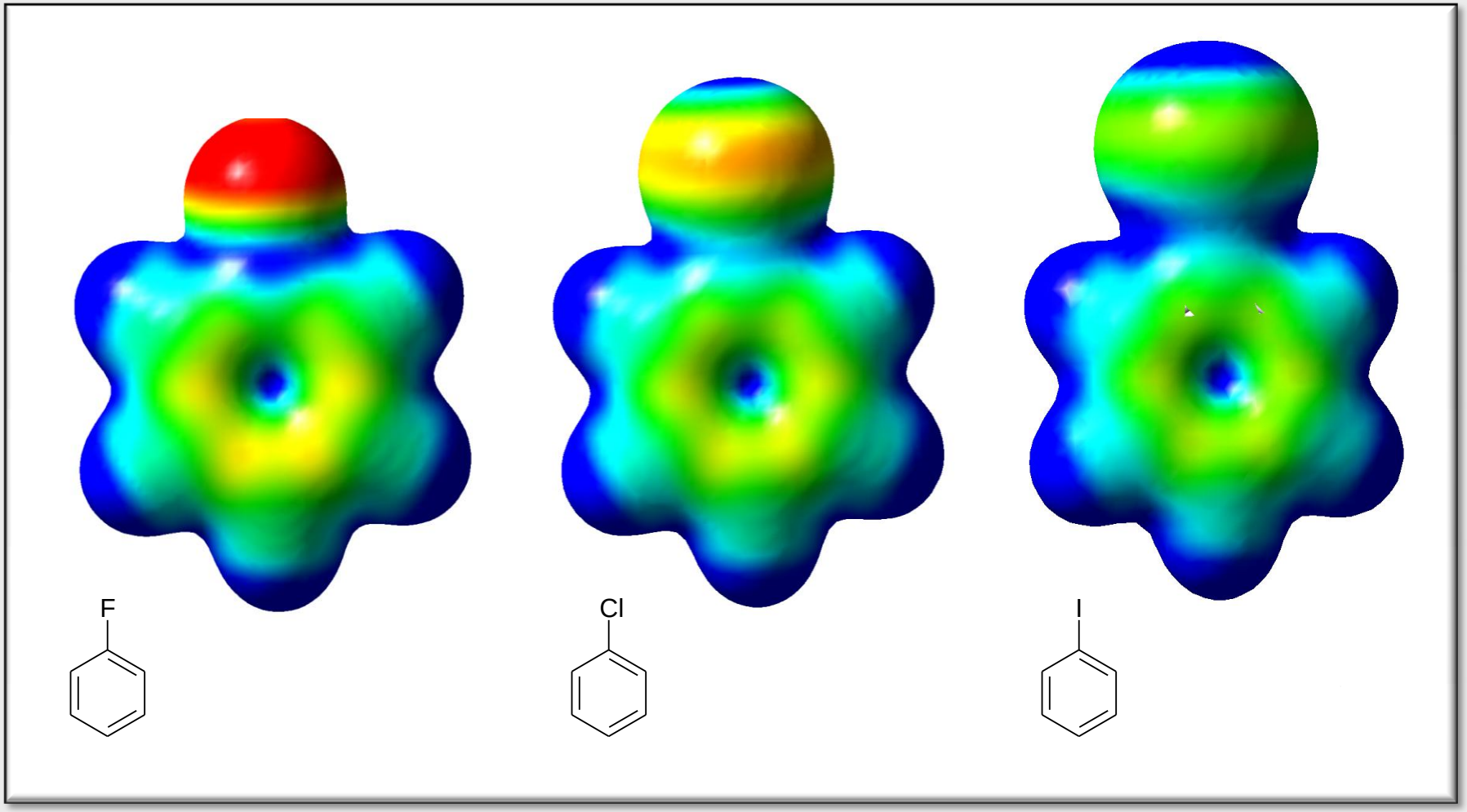
The distribution of charges in the atomic shell gives rise to attractive or repulsive forces between atoms.



High-level Quantum Mechanics Calculations

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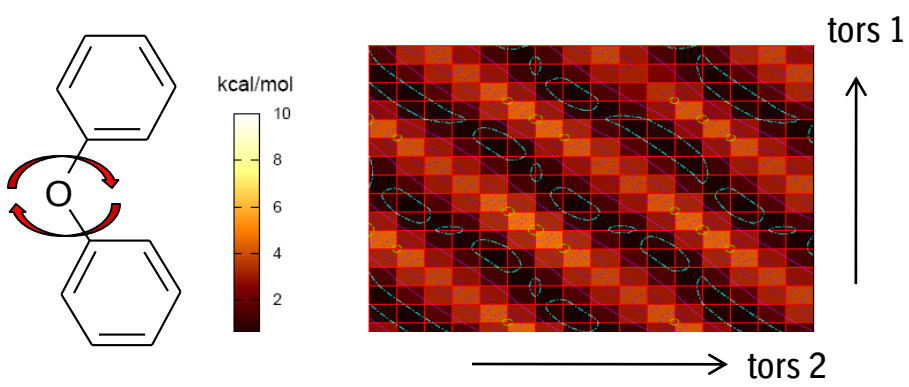
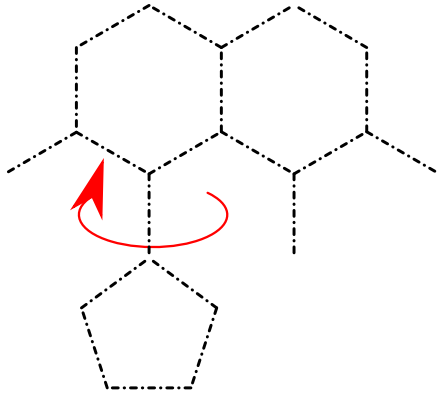
Small molecules need to adopt a certain conformation in order to fit into the binding site of the protein. Is this conformation accessible at body temperature ?

Systematic conformational analyses: fragments of molecules





Example 1: 2D torsional scan
30° steps each
169 parallel jobs
Density functional theory, 6-31 G*
vacuum

Example 2: 1D torsional scan
~20 heavy atoms
Density functional theory, 6-31 G*
vacuum
10° steps, full optimization at each step
per optimization: up to 30 h on 8 CPUs.

Molecular Dynamics Simulations: Flexibility of Biomolecules

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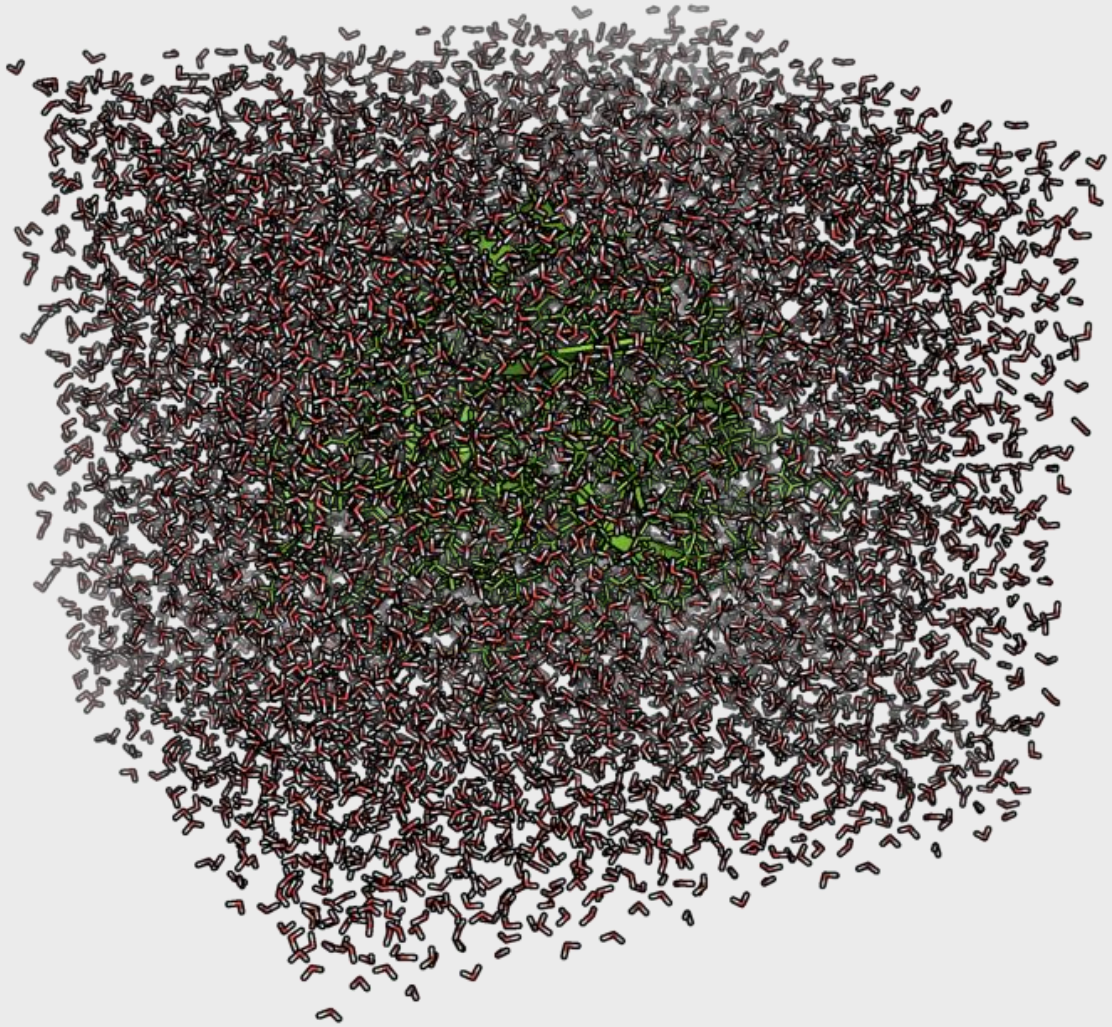

Molecular dynamics simulations:

Follow the thermal movement of each atom within the force field of all other atoms up to several 100 nanoseconds.

- All atoms are treated as individual particles: 10^2-10^5 atoms.
- The simulation obeys Newton's equation of motion.

We want to assess
- conformational substates of proteins
- the stability of ligand binding modes
- free energies of binding, ...

Molecular Dynamics Simulations: Flexibility of Biomolecules

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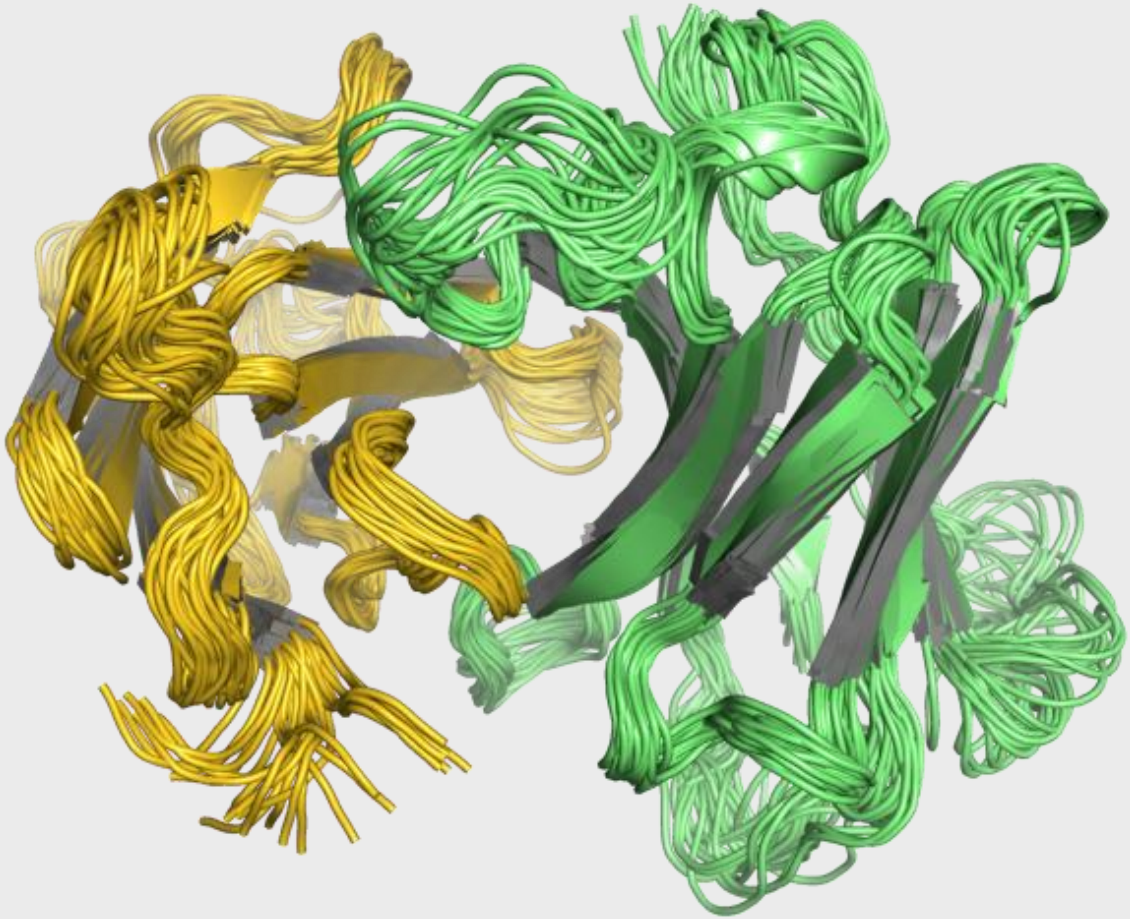

Computation time: 2-3 days on 64 CPUs

Molecular Dynamics Simulations: Flexibility of Biomolecules

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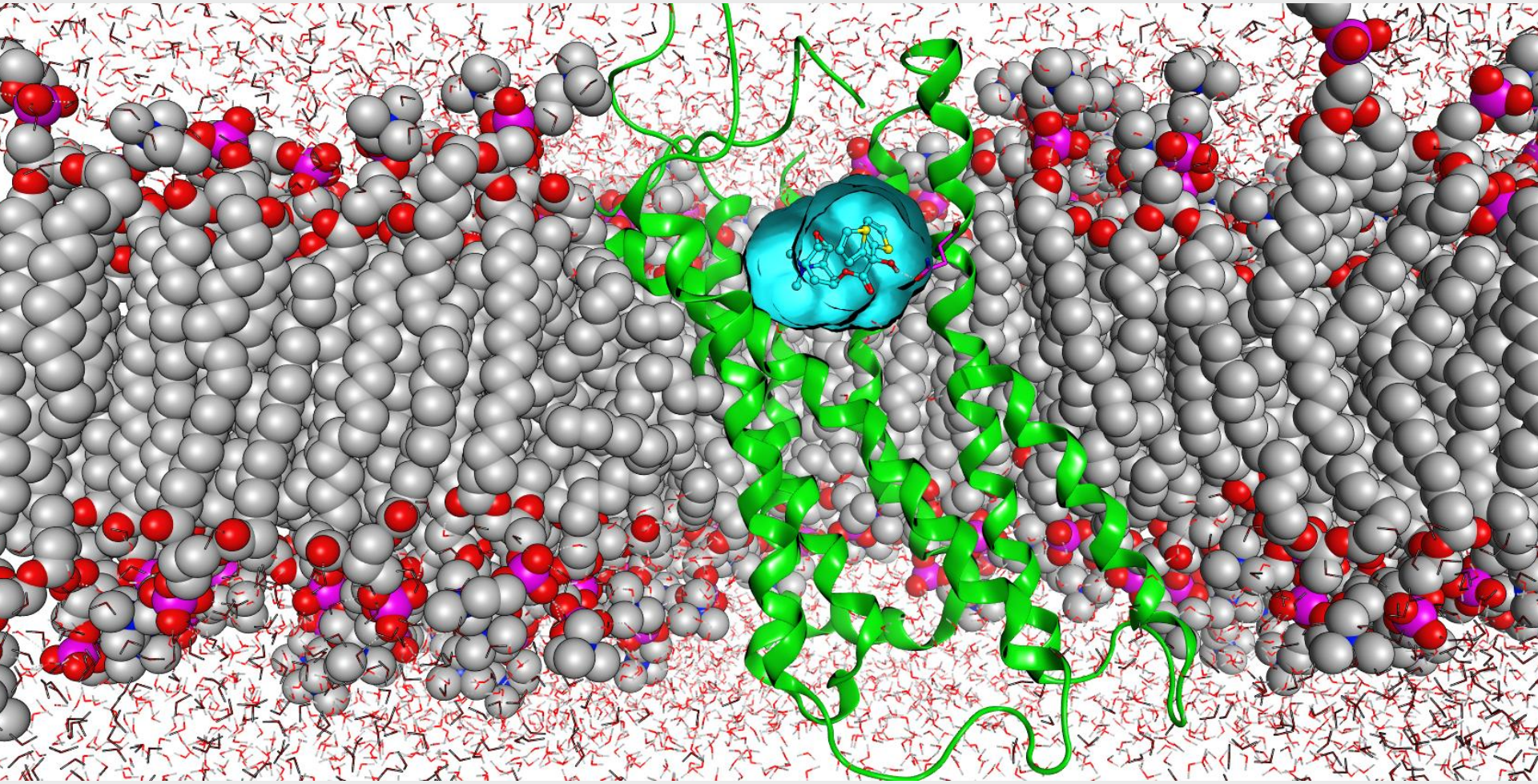

Tiotropium (**Spiriva**®) in the human M3 receptor (model)

66877 atoms
10093 water molecules
282 amino acids (hM3 receptor)
2 ns/day on 8 CPUs
238 phosphodilipids
24382 heavy atoms

HPC Setup

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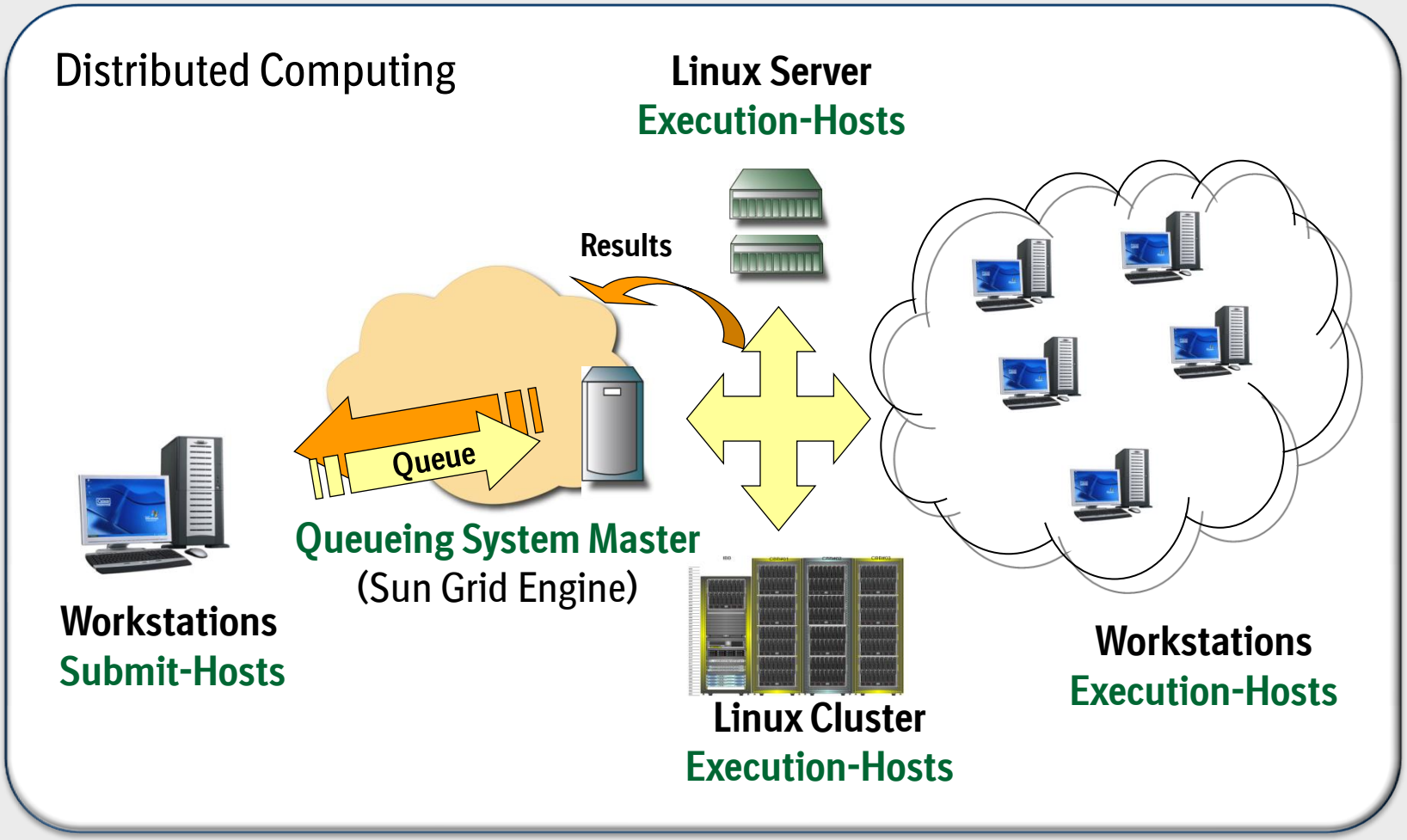

Massive, trivial parallelization: chunks of compounds are processed in parallel
Multiple, simultaneous access to file system for I/O (high throughput storage).

In-silico profiling of molecules
Know the ugly early on

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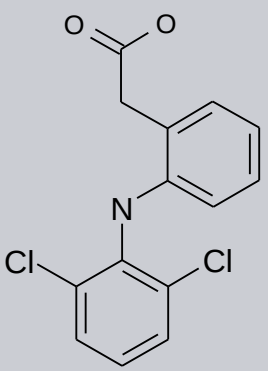
Parameters like metabolic stability, solubility and many others are closely linked to molecular properties. In-silico surrogates are applied to get a first assessment of these parameters.

molecule	ID	XlogP	pKa	H_don
	Diclofenac	4.4	3.9	2

HPC setup

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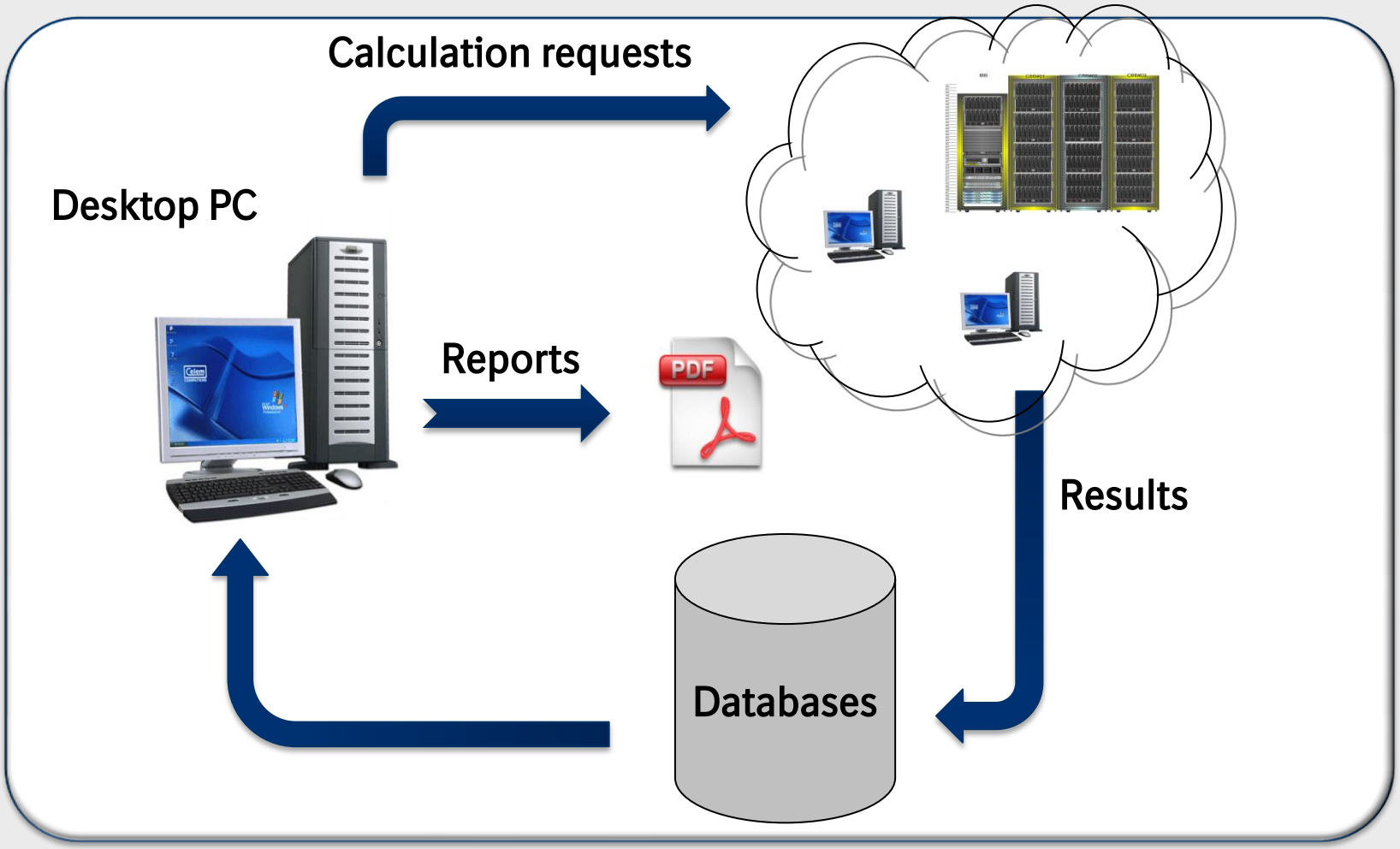

For a complete in-silico profile many different prediction engines must be managed in parallel. The results from all the individual models are then gathered and reported back to the sender.

HPC @ BI (Biberach)
High Perfomance Computing Cluster (4th generation)

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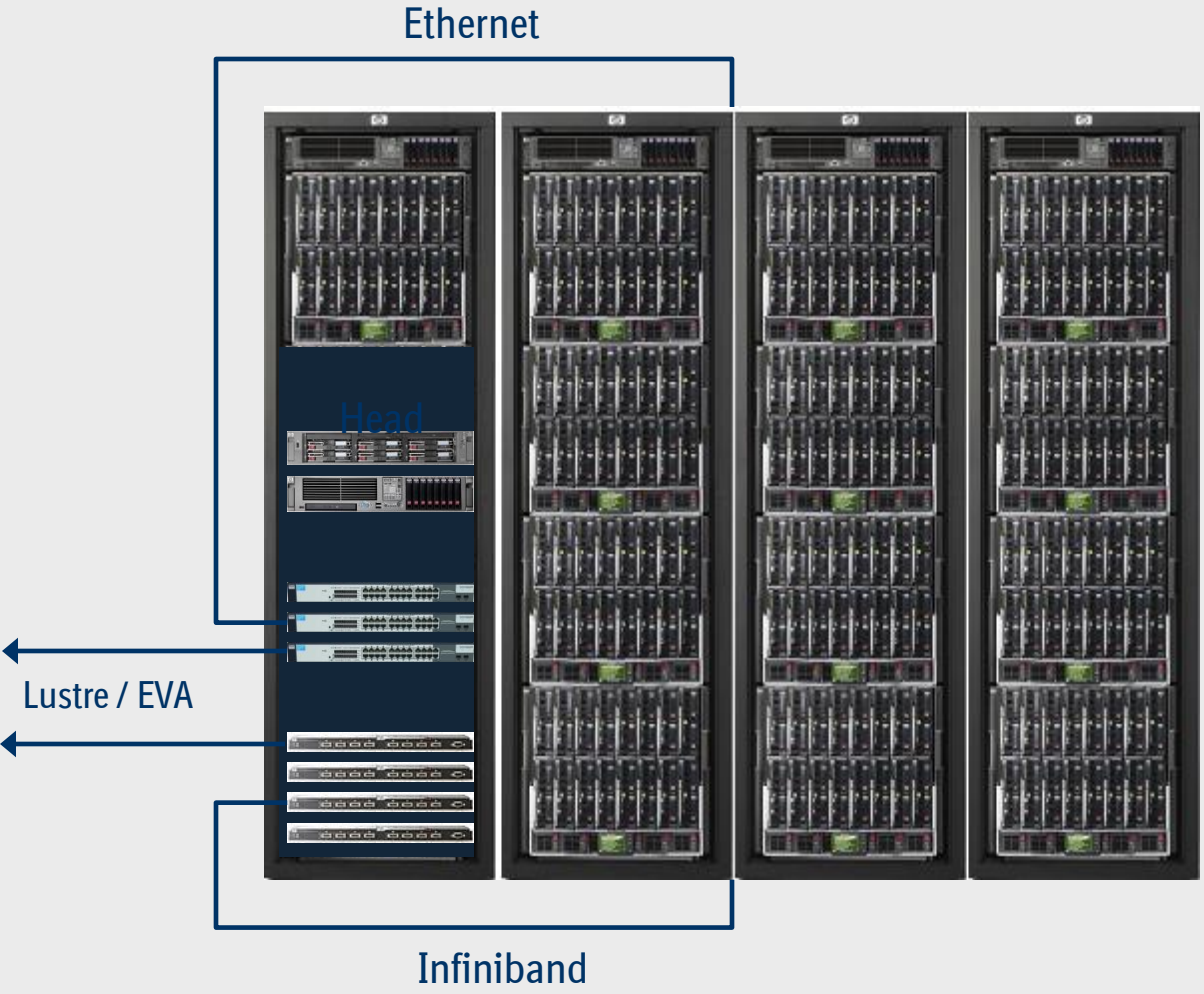

1664 CPUs:

- 13 Enclosures à 16 blades
- 8 CPU-Cores per blade

- Infiniband/Ethernet
- Lustre and EVA storage

Summary

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- An efficent HPC environment is key to CompChem in Pharma Research.
- The applications are highly diverse, ranging from RAM and CPU demanding tasks to thousands of short tasks which are massively parallelized.
- Short response times are indispensable to feed CompChem work into the iterative design cycles of drug discovery programs.
- Execution of heterogenous scientific software requires a flexible HPC environment.

Future Perspective

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- A high need for enhanced compute power is foreseen because
  - the complexity of the systems under investigation increases.
  - more accurate, yet computationally more demanding methods like QM/MM or ultra-long MDs will continue to mature.

- An increase of at least two orders of magnitude will be necessary to fully establish these methods in the drug discovery process, together with novel methods to analyze and aggregate the continuously growing data heap.

- Investment and maintenance costs need to be kept at an affordable level.

- Modern HPC requires a sustainable concept for energy consumption.

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