Development of efficient multiscale methods and extrapolation techniques for multiphysics molecular chemistry

Étienne Polack

Doctoral research project defence, January 2022

Chemistry

Chemistry science of matter and its elements;

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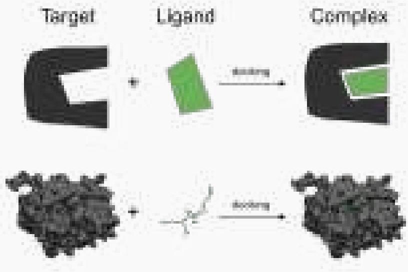
Molecular docking



Interest for drug design applications

- Need for predictive models

https://commons.wikimedia.org/wiki/File:Docking_representation_2.png

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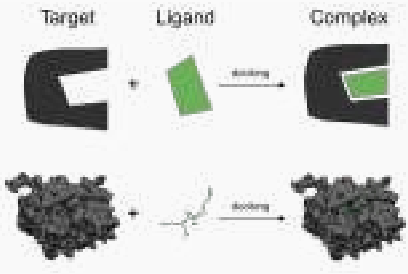

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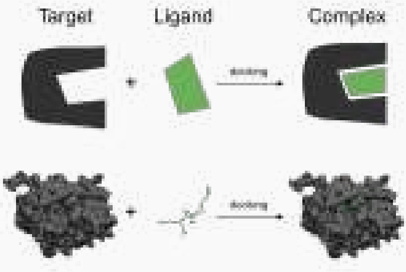

Interest for drug design applications

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→ Quick increase in complexity

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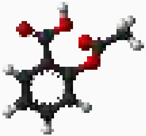
Molecular dynamics simulations and multiscale physics

Time

System size

Molecular dynamics simulations and multiscale physics

Time	fs–ps
	Quantum mechanics 
System size	fm–nm

SCHRÖDINGER equation: *ab-initio*, high accuracy, nuclei and electrons

- Density functional theory (DFT)
- (post-)HARTREE–FOCK (HF) methods

Thousand of atoms

https://commons.wikimedia.org/wiki/File:Aspirin-B-3D-balls.png

Molecular dynamics simulations and multiscale physics

Time	fs–ps	ns–µs
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	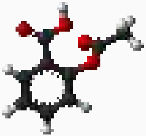	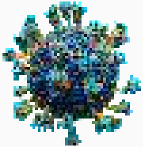
System size	fm–nm	nm–µm

NEWTON equation: parameterised through force fields, medium accuracy, only nuclei

- AMBER
- CHARMM
- AMOEBA

Millions of atoms

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https://commons.wikimedia.org/wiki/File:Coronavirus._SARS-CoV-2.png

Molecular dynamics simulations and multiscale physics

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	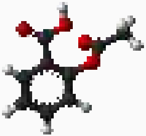	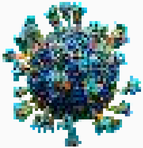	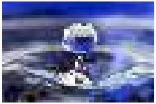
System size	fm–nm	nm–µm	µm–mm

Interaction with an electric field to model solvent

- COSMO

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	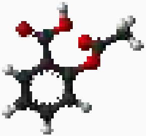	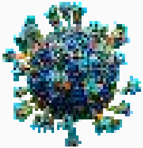	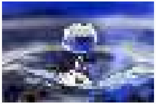
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Focus

Context QM/MM(AMOEBA), multiphysics quantum mechanics/molecular mechanics coupling

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	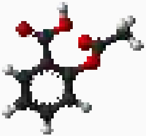	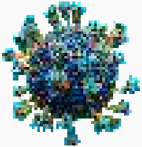	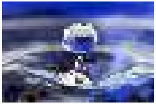
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	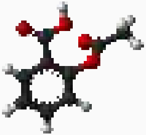	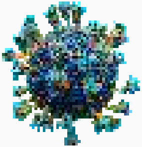	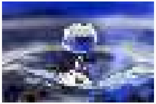
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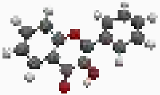
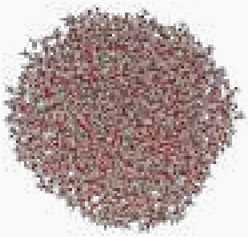
 + 2503×  = 

Outline

+

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Goal Speeding-up QM/MM(AMOEBA) multiscale ab-initio molecular dynamics

+ 2503×

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Outline

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I Speeding-up quantum mechanics simulations

II Speeding-up classical mechanics simulations

Not discussed: *Polarisable classical molecular dynamics*, *Multiscale ab-initio molecular dynamics* and *Extrapolation using the magic points method* (chapters II, III and V)

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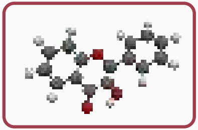

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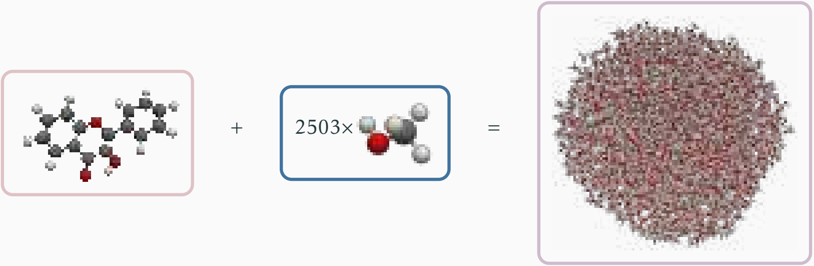

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The time-independent Schrödinger equation

- Molecular system[1] with
  - M nuclei of charge Z_k at positions $\mathbf{R}_k$
  - N electrons of charge -1 au

[1] No particles' spins, Born–Oppenheimer approximation.

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Electronic density

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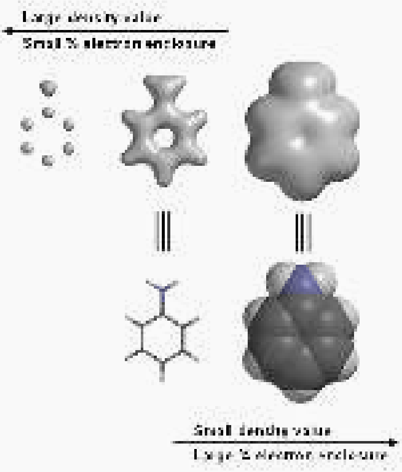

https://commons.wikimedia.org/wiki/File:ElectronDensityAniline.PNG

Equation with density *unknown*

Kohn–Sham model

Equation with density *unknown*, but existence of a functional by Hohenberg–Kohn *theorem*

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Kohn–Sham functional

$$\inf_{\rho} \left\{ \mathcal{E}_{KS}(\rho) := \underbrace{T_{KS}(\rho) + J(\rho) + E_{xc}(\rho)}_{\mathcal{F}(\rho)} + \int \rho V \,\middle|\, \rho \geq 0,\ \rho^{1/2} \in \mathrm{H}^1(\mathbb{R}^3),\ \int \rho = N \right\}$$

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- External potential (interaction with nuclei)
- Approximation of the kinetics energy
- Approximations of the repulsive electronic energy
- Exchange-correlation energy functional (approximations)

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Rewritten nonlinear eigenproblem[1]

Find N lowest eigenvalues and molecular orbitals solving the nonlinear equations

$$\underbrace{\left(-\frac{1}{2}\Delta + v_{KS}[\rho](\mathbf{r})\right)}_{\mathcal{H}_{KS}[\rho]}\phi_i(\mathbf{r}) = \varepsilon_i \phi_i(\mathbf{r}), \quad \text{for } i \in [\![1\,..\,N]\!]$$

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[1] Euler–Lagrange on energy functional

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N problems on $\mathrm{L}^2(\mathbb{R}^3, \mathbb{C})$ instead of one problem on $\mathrm{L}^2(\mathbb{R}^{3N}, \mathbb{C})$

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Equation with density *unknown*, but existence of a functional by Hohenberg–Kohn *theorem*

Kohn–Sham functional

$$\inf_{\rho}\left\{\mathcal{E}_{KS}(\rho) := \underbrace{T_{KS}(\rho) + J(\rho) + E_{xc}(\rho)}_{\mathcal{F}(\rho)} + \int \rho V \,\middle|\, \rho \geq 0,\ \rho^{1/2} \in \mathrm{H}^1(\mathbb{R}^3),\ \int \rho = N\right\}$$

Rewritten nonlinear eigenproblem[1]

Find N lowest eigenvalues and molecular orbitals solving the nonlinear equations

$$\underbrace{\left(-\frac{1}{2}\Delta + v_{KS}[\rho](\mathbf{r})\right)}_{\mathcal{H}_{KS}[\rho]}\phi_i(\mathbf{r}) = \varepsilon_i\phi_i(\mathbf{r}), \quad \text{for } i \in [\![1\,..\,N]\!]$$

in $\mathcal{W}_N := \left\{\Phi := (\phi_1, \dots, \phi_N) \in \mathrm{L}^2(\mathbb{R}^3, \mathbb{C})^N \,\middle|\, \langle\phi_i, \phi_j\rangle = \delta_{ij}, 1 \leq i, j \leq N\right\}$

N problems on $\mathrm{L}^2(\mathbb{R}^3, \mathbb{C})$ instead of one problem on $\mathrm{L}^2(\mathbb{R}^{3N}, \mathbb{C})$

Electronic density $\rho(\mathbf{r}) = 2\sum_{i=1}^{N}|\phi_i(\mathbf{r})|^2$

[1] Euler–Lagrange on energy functional

Discretisation of the KOHN–SHAM equations

GALERKIN approximation of $\mathsf{L}^2(\mathbb{R}^3, \mathbb{C})$: $\mathcal{V} := \mathrm{Span}(\chi_1, \dots, \chi_{\mathcal{N}}) \subset \mathsf{L}^2(\mathbb{R}^3, \mathbb{C})$, with χ_μ Gaussian type orbitals, centered on the atoms

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Solutions as linear combination of atomic orbitals (LCAO)

$$\Phi \in \mathcal{V}^N \Rightarrow \phi_i(\mathbf{r}) := \sum_{\mu=1}^{\mathcal{N}} C_{\mu i} \chi_\mu(\mathbf{r}), \quad i \in [\![1 \,..\, N]\!]$$

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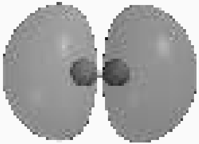

https://commons.wikimedia.org/wiki/File:Dihydrogen-phase-3D-balls.png

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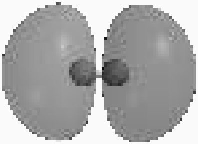

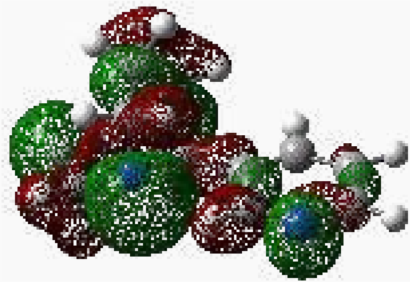

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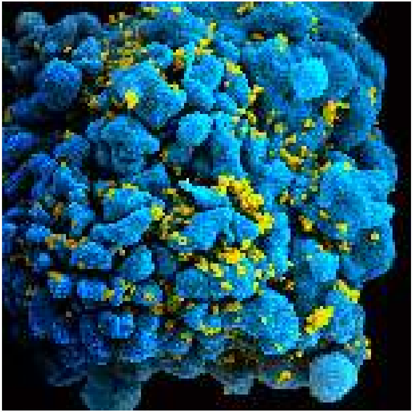
https://commons.wikimedia.org/wiki/File:Nicotine_(HOMO-LUMO).png

Classical molecular dynamics

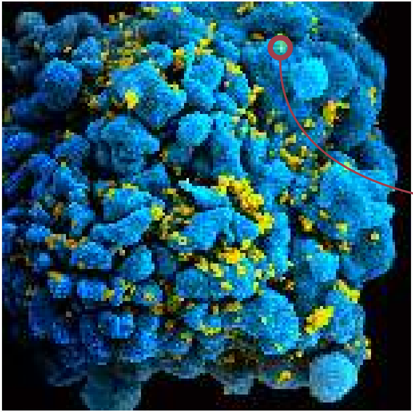
Human immunodeficiency virus 1 (≈ 100 nm) on T cell (≈ 5 µm)

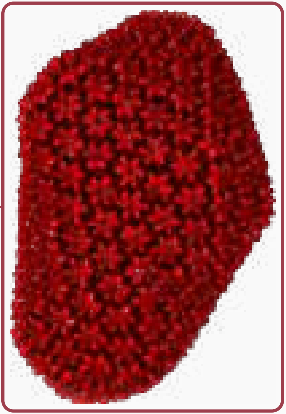


https://commons.wikimedia.org/wiki/File:HIV_H9_T-cell.jpg

Classical molecular dynamics

Human immunodeficiency virus 1 (≈ 100 nm) on T cell (≈ 5 µm), capsid (≈4 mil. atoms)





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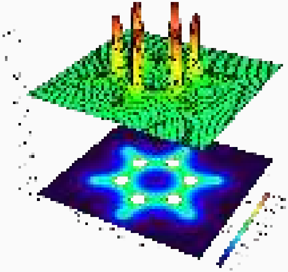
https://commons.wikimedia.org/wiki/File:Protein_Imager_high_quality_illustration_example_1_HIV_capsid.png

Classical molecular mechanics

Cannot account for electrons

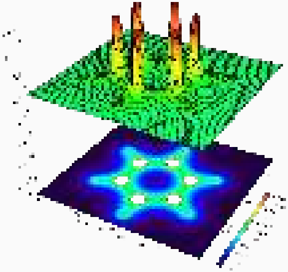


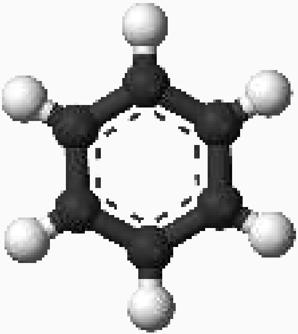
Benzene C_6H_6

https://commons.wikimedia.org/wiki/File:Elektronendichtedarstellungen_von_Benzol.png

Classical molecular mechanics

Cannot account for electrons; replaced by notion of (parameterised) chemical bounds





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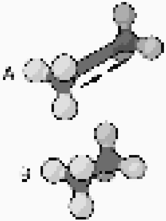
Force fields

Force fields Choices of representation (intra- and intermolecular terms) along with parameterisations



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https://commons.wikimedia.org/wiki/File:Bond_stretching_energy.svg

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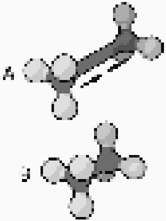

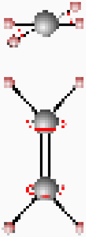

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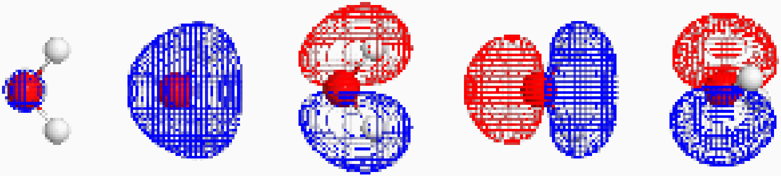
https://commons.wikimedia.org/wiki/File:Torsionsschwingung_ethylen.png

Molecular orbitals of water (quantum mechanics)



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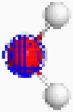

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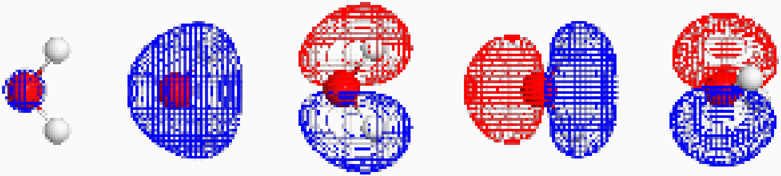

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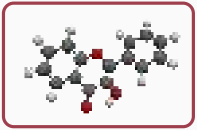
AMOEBA model Polarisable force field with static multipoles up to quadrupoles, implemented in `TINKER`

Speeding-up quantum mechanics simulations



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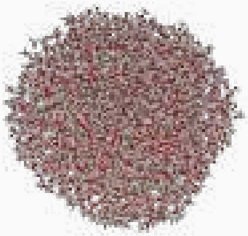

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- N electrons
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Self-consistent field equations

Find $C \in \mathcal{M}$ and diagonal matrix $E \in \mathbb{R}^{N\times N}$ such that

$$\begin{cases} H_{KS}(D)C = SCE \\ C^\mathsf{T}SC = \mathrm{Id}_N \\ D = CC^\mathsf{T} \end{cases},$$

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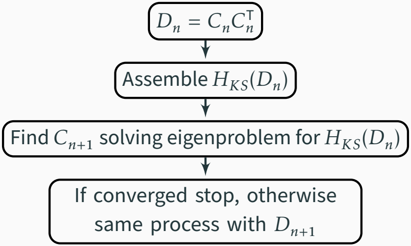

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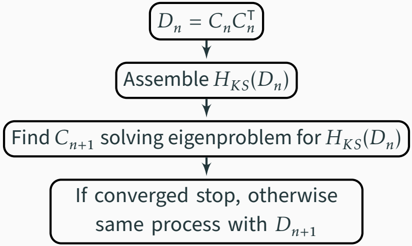

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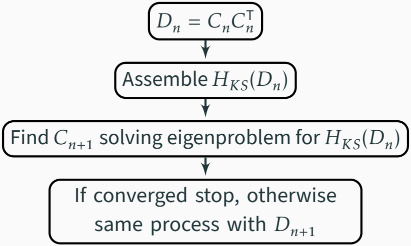

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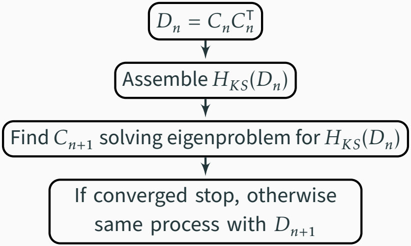

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…or provide algorithm with a good initial guess C_0.

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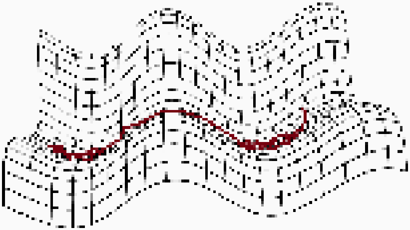

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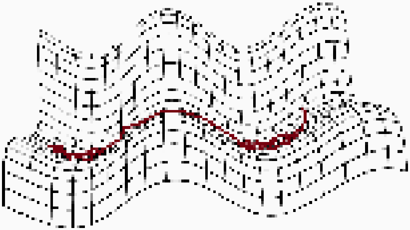


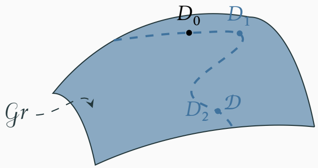
Simple scheme thanks to LCAO: at time-step t^{k+1}, use previous converged density D_n^k

Aim

Fewer self-consistent field iterations on same molecular system using appropriate initial guess

Up to normalisation, density matrices are points on a Grassmannian manifold

$$S^{1/2} D S^{1/2} \in \mathcal{G}r := \left\{ D \in \mathbb{R}^{\mathcal{N}\times N} \,\middle|\, D = D^{\mathsf{T}}, D^2 = D, \mathrm{Tr}(D) = N \right\}.$$



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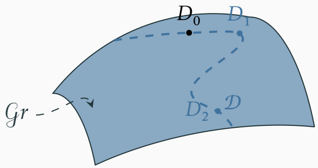

Classical linear combinations extrapolation scheme: objects not on manifold!

$$\sum c_i D_i \notin \mathcal{G}r$$

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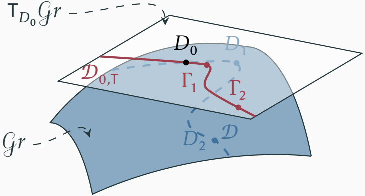

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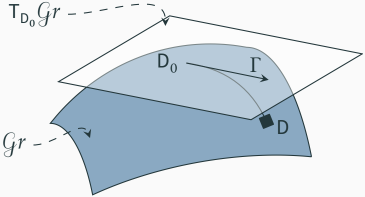
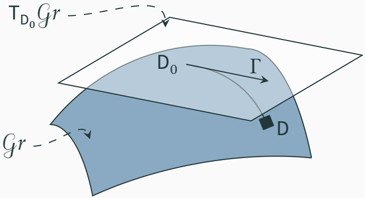
Let's use the tangent space!



Local diffeomorphism between manifold $\mathcal{G}r$ and affine space, the tangent space, cheap to compute



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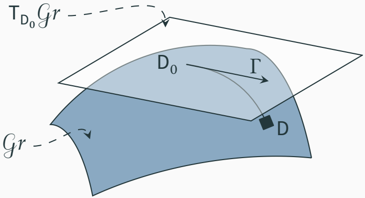
- Exponential function

$$\begin{aligned}\mathrm{Exp}_{\mathcal{G}r,0} : \mathsf{T}_{D_0}\mathcal{G}r &\to \mathcal{G}r \\ \Gamma &\mapsto CC^{\mathsf{T}},\end{aligned}$$

where $C = [C_0 V \cos(\Sigma) + U \sin(\Sigma)]V^{\mathsf{T}}$, with $\Gamma = U\Sigma V^{\mathsf{T}}$ the singular value decomposition of Γ



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- Logarithm function

$$\begin{aligned}\mathrm{Log}_{\mathcal{G}r,0} : \mathcal{G}r &\to \mathsf{T}_{D_0}\mathcal{G}r \\ D &\mapsto \mathrm{Log}_{\mathcal{G}r,0}(D)\end{aligned}$$

  defined similarly

Method's constraints

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- Flexible and as simple as possible for end users

The G-Ext method — Molecular descriptors

Each time-step, nuclei's positions for *free*; we want the corresponding density matrices $D_{\mathbf{R}}$

Molecular descriptors

$$\begin{aligned} \mathbb{R}^{3M} &\to \mathcal{G}r(N, \mathcal{N}) \\ \mathbf{R} &\mapsto D_{\mathbf{R}} \end{aligned}$$

The G-Ext method — Molecular descriptors

Each time-step, nuclei's positions for *free*; we want the corresponding density matrices $D_{\mathbf{R}}$

We want linear combinations on tangent space, and density matrices as initial guesses

Molecular descriptors

$$\begin{aligned} \mathbb{R}^{3M} &\to \mathsf{T}_{D_{\mathbf{0}}}\mathcal{G}r \to \mathcal{G}r(N,\mathcal{N}) \\ \mathbf{R} &\mapsto \quad \Gamma_{\mathbf{R}} \quad \mapsto D_{\mathbf{R}} = \mathrm{Exp}_{\mathcal{G}r,0}(\Gamma_{\mathbf{R}}) \end{aligned}$$

$$\mathbf{R} \mapsto \Gamma_{\mathrm{app}}(\mathbf{R}) = \sum_{i=1}^{N_t} c_{\mathbf{R},i}\,\Gamma_{\mathbf{R}(t_i)} \in \mathsf{T}_{D_{\mathbf{0}}}\mathcal{G}r$$

The G-Ext method — Molecular descriptors

Each time-step, nuclei's positions for *free*; we want the corresponding density matrices $D_{\mathbf{R}}$

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Map should take advantages of properties of the density matrices (*e.g.*, translation invariance)

Molecular descriptors $d_{\mathbf{R}}$

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Notion from machine learning

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Coulomb matrix at time-step t_k

$$(d_{\mathbf{R}})_{ij} = \begin{cases} 0.5 Z_i^{2.4} & \text{if } i = j \\ \dfrac{Z_i Z_j}{|\mathbf{R}^i(t_k) - \mathbf{R}^j(t_k)|} & \text{otherwise} \end{cases}$$

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G-Ext method we developed

- Use of molecular descriptors
- Linear approximation on tangent space
- Retraction on manifold $\mathcal{G}r$

The G-Ext method — Least-squares

We want coefficients $c_{\mathbf{R},i}$ that can approximate the density matrices on the tangent space

$$\mathbf{R} \mapsto \Gamma_{\mathrm{app}}(\mathbf{R}) = \sum_{i=1}^{N_t} c_{\mathbf{R},i}\, \Gamma_{\mathbf{R}(t_i)} \in \mathsf{T}_{D_{\mathbf{0}}}\mathcal{G}r$$

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Least-squares method to solve

$$\min_{c_{\mathbf{R}} \in \mathbb{R}^{N_t}} \left| d_{\mathbf{R}} - \sum_{i=1}^{N_t} c_{\mathbf{R},i} d_{\mathbf{R}(t_i)} \right|^2$$

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We use the same coefficients for density matrices on the tangent space and use the retracted density matrix

$$D_{\mathrm{app}}(\mathbf{R}) = \mathrm{Exp}_{\mathcal{G}r,0}\left(\sum_{i=1}^{N_t} c_{\mathbf{R},i}\, \Gamma_{\mathbf{R}(t_i)} \right)$$

as an initial guess to the self-consistent field algorithm

Molecular system	Quantum atoms	Classical atoms	$\mathcal{N}$
OCP	129	4915	1038
APPA	31	16 449	309
DMABN	21	6843	185
3HF	28	15 018	290

OCP: orange carotenoid protein

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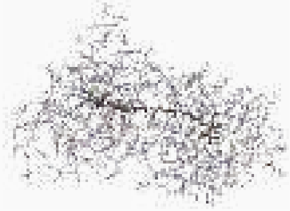

OCP: orange carotenoid protein

- 10^{-5} root-mean-square
- 1 ps dynamics
- 0.5 fs time-step
- ref. method

	OCP		DMABN		APPA		3HF	
Method	Average	σ	Average	σ	Average	σ	Average	σ
XLBO	3.82	0.66	3.98	0.16	3.00	0.03	4.00	0.14
XLBO/MW	2.95	0.31	3.76	0.56	3.00	0.34	3.96	0.31
G-Ext(3)	2.57	0.84	3.54	0.78	2.95	0.50	3.09	0.41
G-Ext(4)	2.48	0.88	3.14	0.62	2.51	0.50	3.25	0.68
G-Ext(5)	2.25	0.96	3.23	0.75	2.51	0.50	3.30	0.72
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Results — Performances

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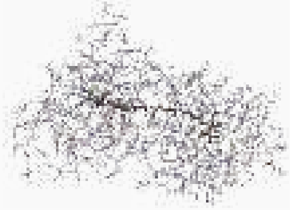

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Decrease in self-consistent field iterations

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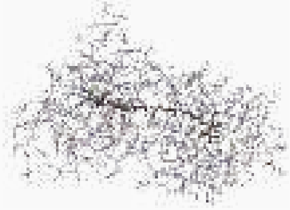

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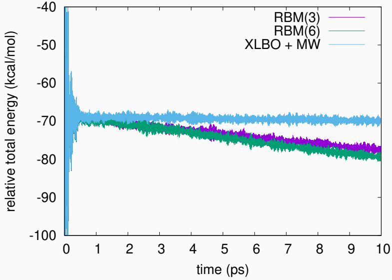
Decrease in self-consistent field iterations; adds up with long molecular dynamics!

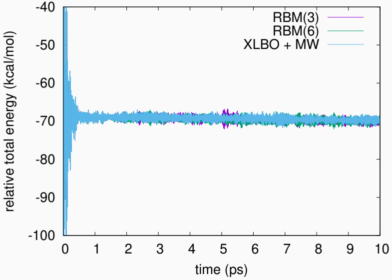
Results — Total energy conservation

- 3HF system
- 10 ps dynamics
- 0.5 fs time-step
- +505 000 kcal/mol shift
- 10^{-5} and 10^{-7} root-mean-square

Relaxed parameters (10^{-5})



Conservative parameters (10^{-7})



Perspectives

Conclusion

Lower number of self-consistent field iterations

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Future work

- Time reversibility

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- Time reversibility
- Geometry optimisation

Perspectives

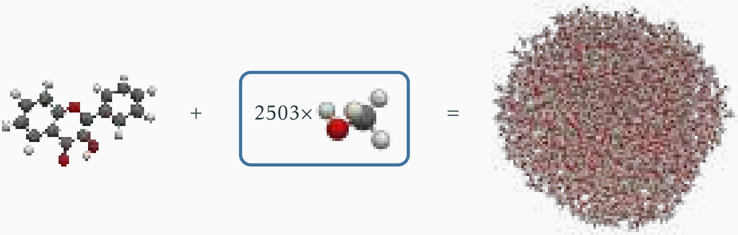
Conclusion

Lower number of self-consistent field iterations

Future work

- Time reversibility
- Geometry optimisation
- Bypass self-consistent field algorithm (*e.g.*, empirical interpolation method for Fock matrices, minimisation on tangent space)

Speeding-up classical mechanics simulations



Molecular system with N nuclei of point charge M_{0i} at positions $\mathbf{r}_i$

N-body problem of computing the electrostatic energy

$$\mathcal{E}_{\mathrm{elec}} := \frac{1}{2} \sum_{1 \leqslant i \neq j \leqslant N} \frac{\mathrm{M}_{0i}\mathrm{M}_{0j}}{|\mathbf{r}_j - \mathbf{r}_i|}.$$

Bottleneck, scales as $\mathcal{O}(N^2)$

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For AMOEBA force field, generalised to (static and non-static) multipoles $\mathbf{M}_n$ with derivation operators $\mathbf{D}_i^n$

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Cuttoff methods not accurate for molecular dynamics because *slow* decrease of the inverse function

Smooth particle mesh EWALD

- Reference method
- Periodic problem
- Smooth function splitting the potential

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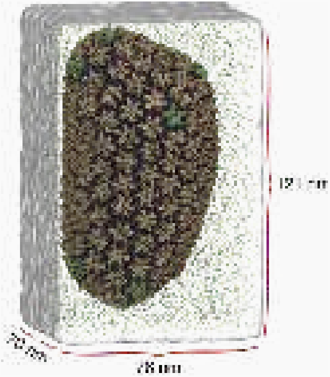

$>$ 64 million atoms, months of computations on thousands of GPUs

Juan R. Perilla and Klaus Schulten. "Physical Properties of the HIV-1 Capsid from All-Atom Molecular Dynamics Simulations". In: *Nature Communications* 8 (July 19, 2017), p. 15959

Fast multipole method

- Linear computational complexity hierarchical method

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- Common in physics

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- Common in physics; less so in chemistry

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- Common in physics; less so in chemistry
- *E.g.*, `ScalFMM` solves N-body problem for point charges

Implementation status

Modification of ScalFMM[1] and TINKER for AMOEBA

[1] P2M, L2P and P2P operators

Implementation status

Modification of ScalFMM[1] and TINKER for AMOEBA

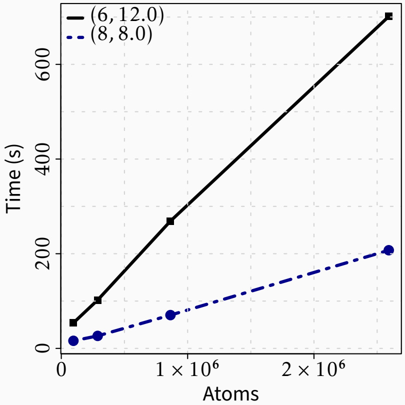
Terms	Potential	Energy	Forces
Charges	•	•	•
Dipoles	✓	✓	✓
Quadrupoles	✓	✓	✓
General multipoles	✓	✗	✗

• present ✓ implemented ✗ not implemented

[1] P2M, L2P and P2P operators

Results — Linear scaling

- Single time-step
- 10^{-5} for polarisation
- 216 cores
- Total execution time of `TINKER(AMOEBA)-ScalFMM`
- Conservative parameters
- Relaxed parameters



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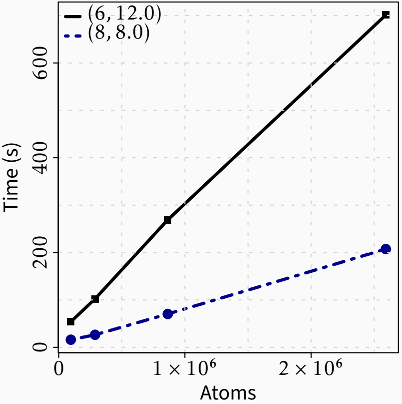

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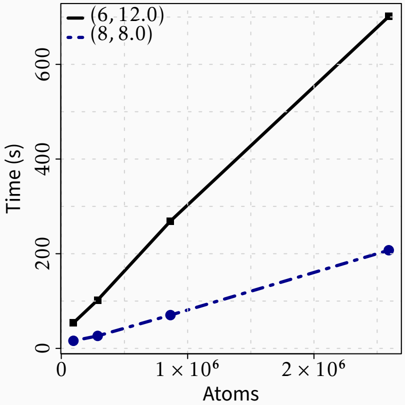
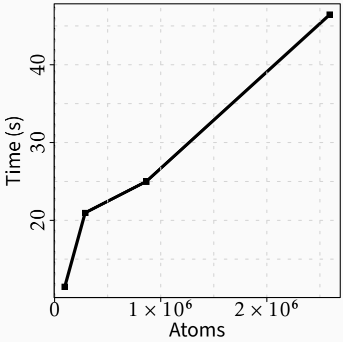


(but expected)

Results — Weak scalability

- No polarisation
- Triple system sizes along cores
- Relaxed parameters
- Total execution time of TINKER(AMOEBA)-ScalFMM



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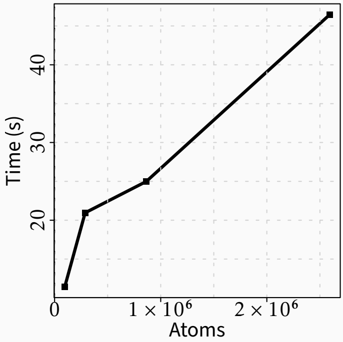

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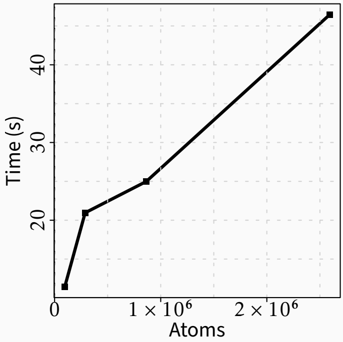


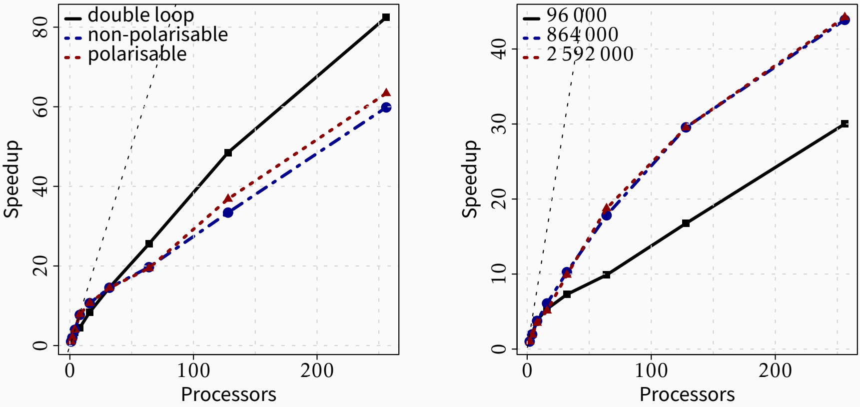
(but expected)

Results — Strong scalability

- Single time-step
- Relaxed set of parameters

Left 96 000 atoms, double loop with `TINKER`

Right Scalability starts at four cores



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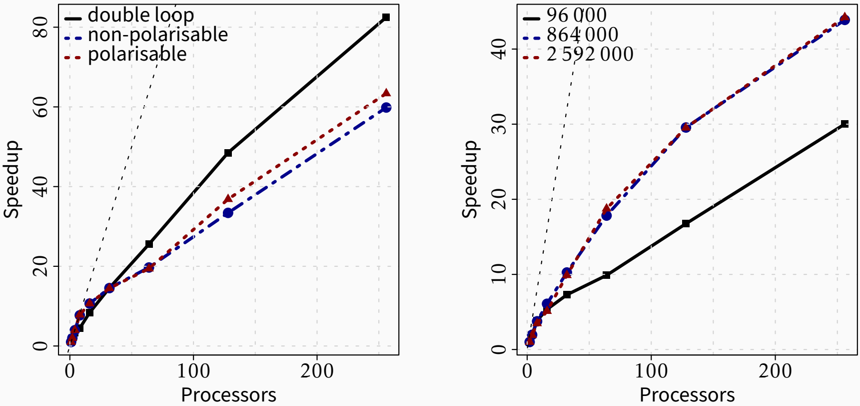

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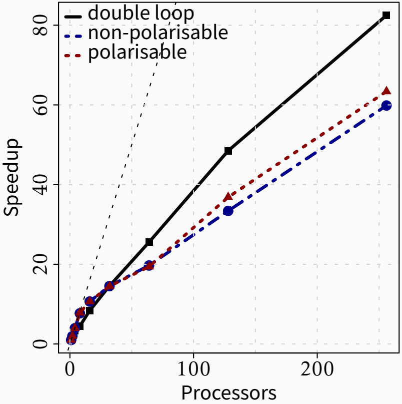
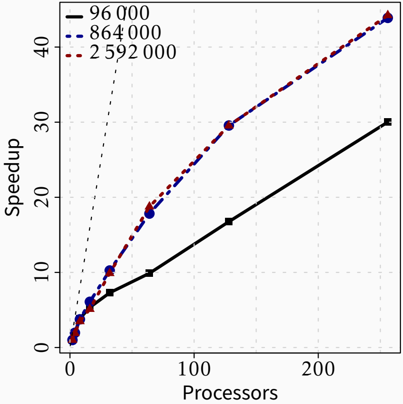
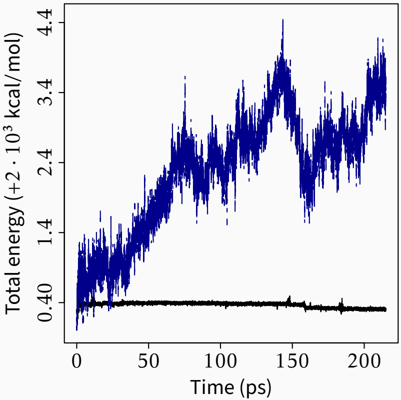




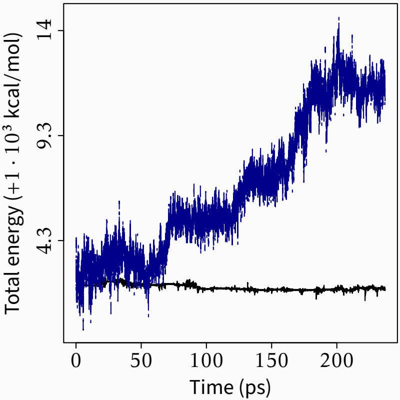
(but not a deal-breaker)

- DHFR system (2489 atoms)
- 0.10 fs time-steps
- Conservative parameters
- Relaxed parameters

Point charges



Static multipoles up to quadrupoles



Results — Energy conservation of non-solvated DHFR

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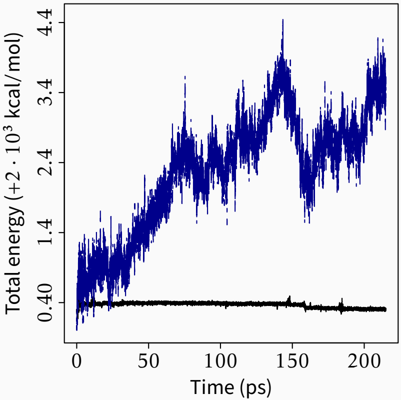
- Conservative parameters
- Relaxed parameters

Point charges



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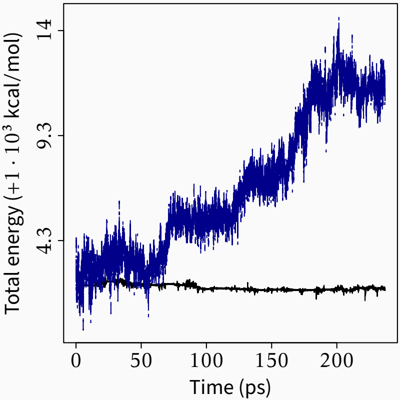
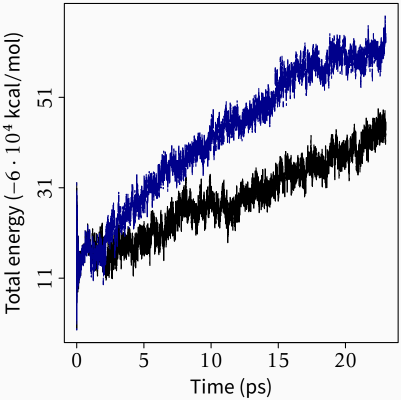


Energy conserved

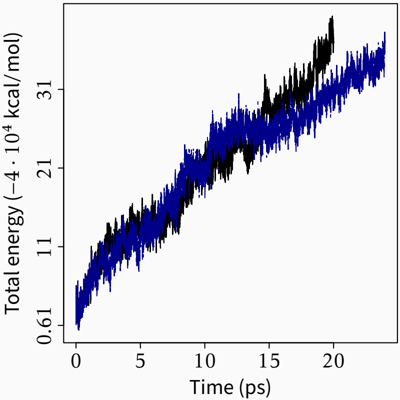
Results — Energy conservation of solvated DHFR

- Solvated DHFR system (23 558 atoms)
- 0.25 fs time-steps
- 10^{-8} for polarisation
- 10^{-5} for polarisation

Conservative parameters



Relaxed parameters



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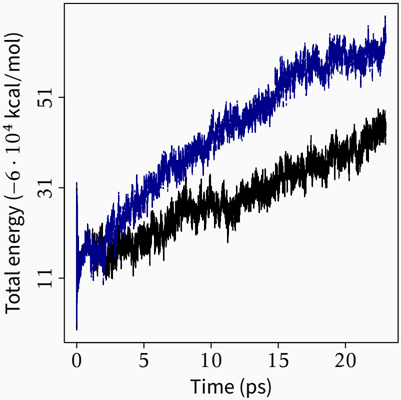

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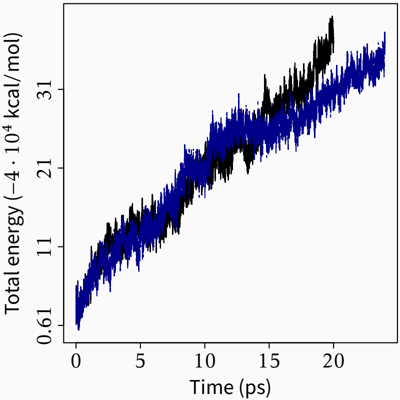

Energy drift

Results — Energy conservation of solvated DHFR

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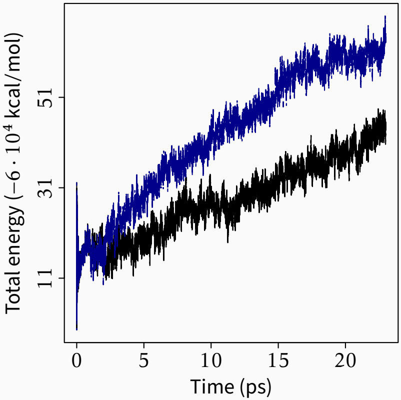
Conservative parameters



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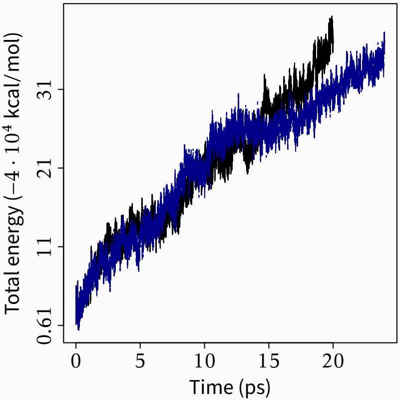

Energy drift (needs investigation)

Perspectives

Conclusion

- Linear scaling for non-periodic systems

Perspectives

Conclusion

- Linear scaling for non-periodic systems
- Straightforward and high-performance implementation

Perspectives

Conclusion

- Linear scaling for non-periodic systems
- Straightforward and high-performance implementation

Future work

- Adaptive grid

Perspectives

Conclusion

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- Periodic case for systematic comparisons to smooth particle mesh EWALD

Perspectives

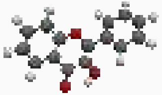
Conclusion

- Linear scaling for non-periodic systems
- Straightforward and high-performance implementation

Future work

- Adaptive grid
- Periodic case for systematic comparisons to smooth particle mesh EWALD
- Real-case tests

Conclusion



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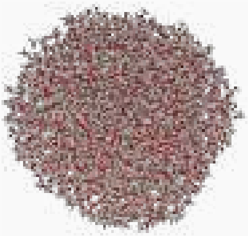
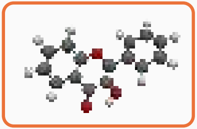


Conclusion



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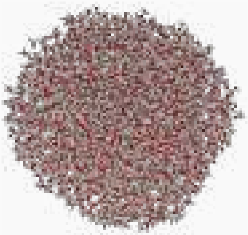
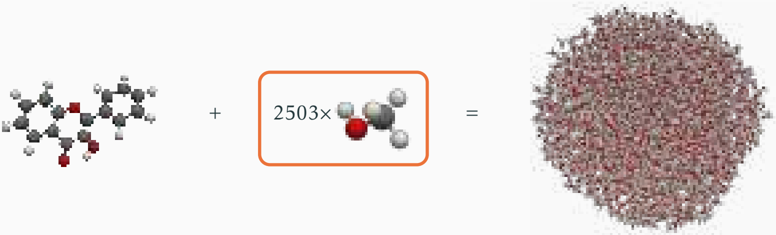


Major results

Decrease in time for densities of quantum atoms

Conclusion



Major results

Decrease in time for densities of quantum atoms and model classical atoms, solvent in particular, with linear complexity on supercomputers

Conclusion

+ 2503×

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Major results

Decrease in time for densities of quantum atoms and model classical atoms, solvent in particular, with linear complexity on supercomputers
⇒ Allows for longer multiphysics QM/MM(AMOEBA) simulations, bigger systems or more solvent for more accurate physics

Thank you for your attention!

Publications

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Lindgren, Eric B. et al. "An Integral Equation Approach to Calculate Electrostatic Interactions in Many-Body Dielectric Systems". In: *Journal of Computational Physics* 371 (Oct. 15, 2018), pp. 712–731.

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Polack, Étienne, Yvon Maday, and Andreas Savin. *FLEIM: A Stable, Accurate and Robust Extrapolation Method at Infinity for Computing the Ground State of Electronic Hamiltonians*. Dec. 24, 2021. URL: `http://arxiv.org/abs/2112.13139`.

Polack, Étienne et al. "An Approximation Strategy to Compute Accurate Initial Density Matrices for Repeated Self-Consistent Field Calculations at Different Geometries". In: *Molecular Physics* 118.19-20 (Oct. 17, 2020), e1779834.

Polack, Étienne et al. "Grassmann Extrapolation of Density Matrices for Born–Oppenheimer Molecular Dynamics". In: *Journal of Chemical Theory and Computation* 17.11 (Nov. 9, 2021), pp. 6965–6973.