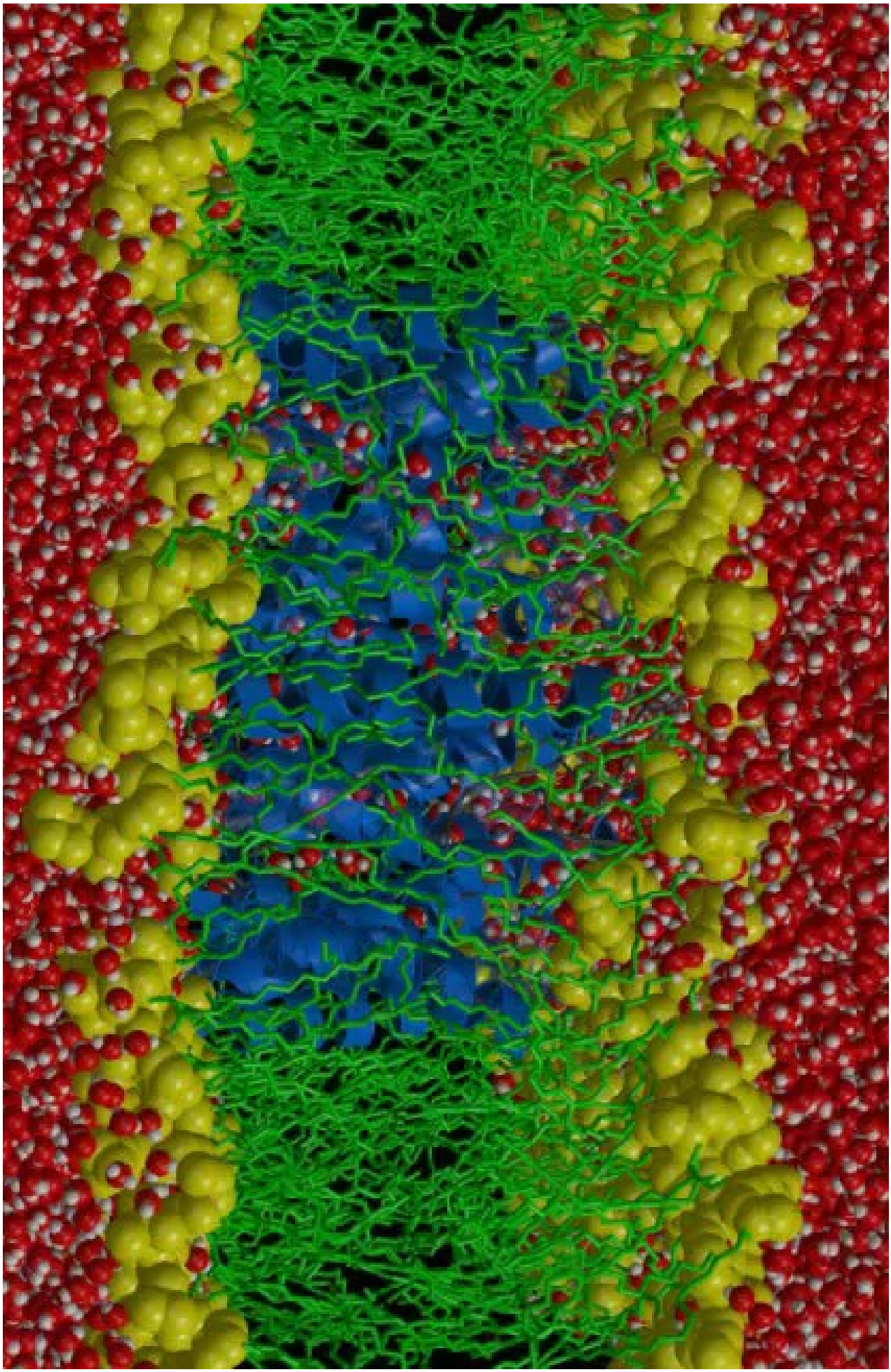
UNIVERSITÄT
HEIDELBERG

Simulations

L9 Structural Bioinformatics

WiSe 2023/24, Heidelberg University



de Groot BL, Grubmüller H. Water permeation across biological membranes: mechanism and dynamics of aquaporin-1 and GlpF. Science. 2001 Dec 14;294(5550):2353-7. doi: 10.1126/science.1066115. PMID: 11743202.

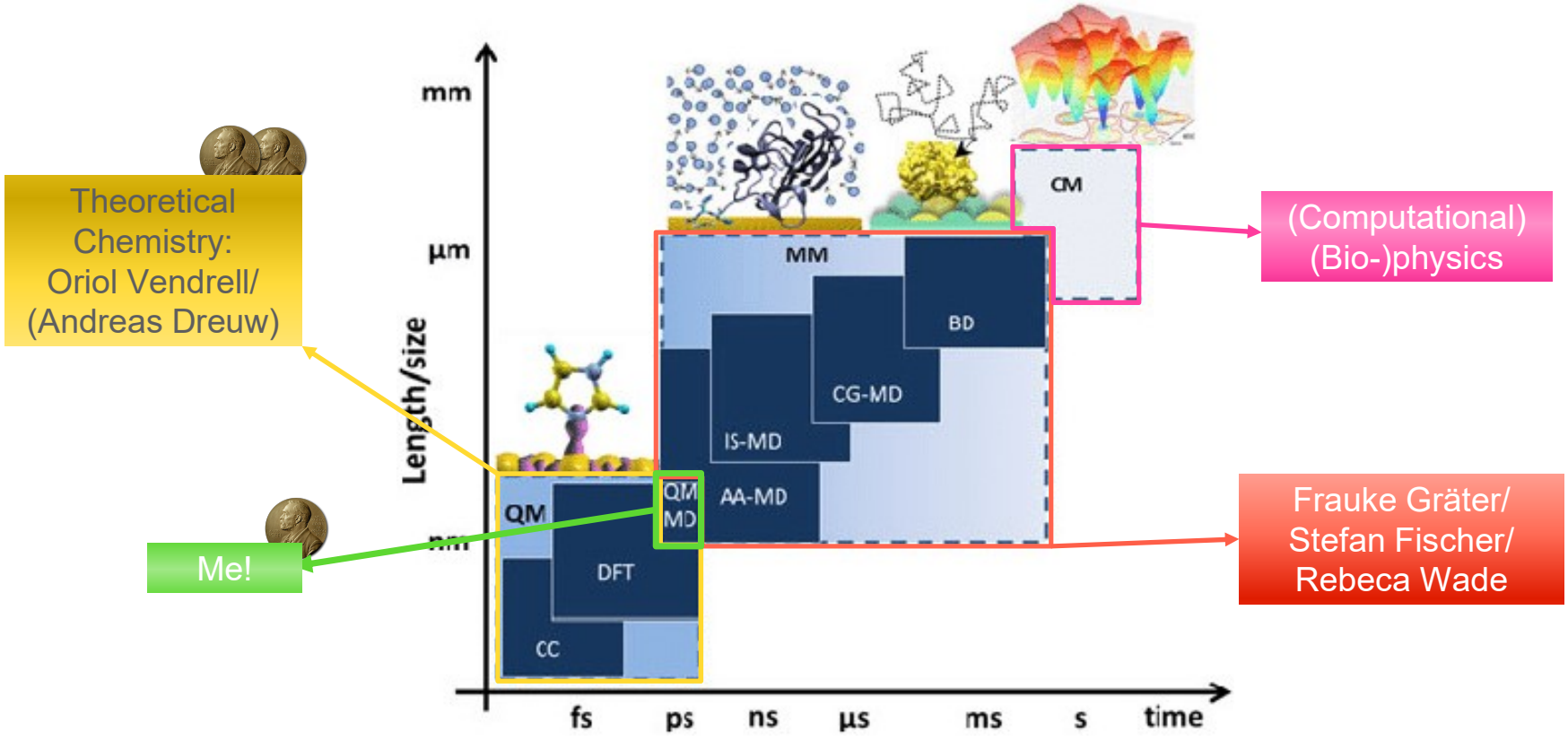
Outline

1. Overview
2. Approximations
3. Force Fields
4. Algorithms
5. Coarse Grained Simulations
6. Recipe
7. Further Studying

1. Overview

Overview

What is possible?

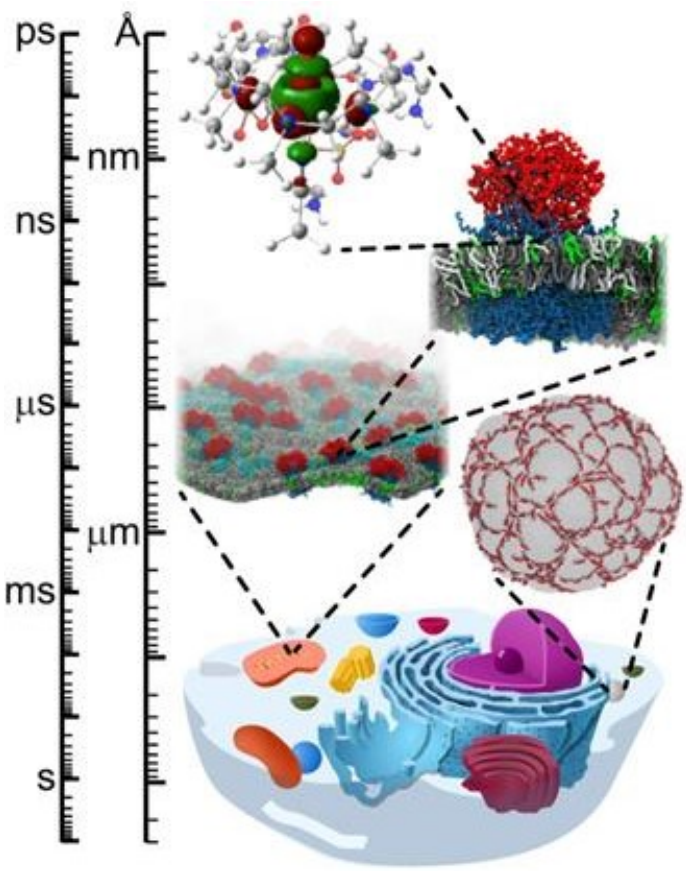


Ozboyaci, M., Kokh, D., Corni, S., & Wade, R. (2016). Modeling and simulation of protein–surface interactions: Achievements and challenges. *Quarterly Reviews of Biophysics, 49*, E4. doi:10.1017/S0033583515000256

„For the development of multiscale models for complex chemical systems“

Overview

Pro-/Con



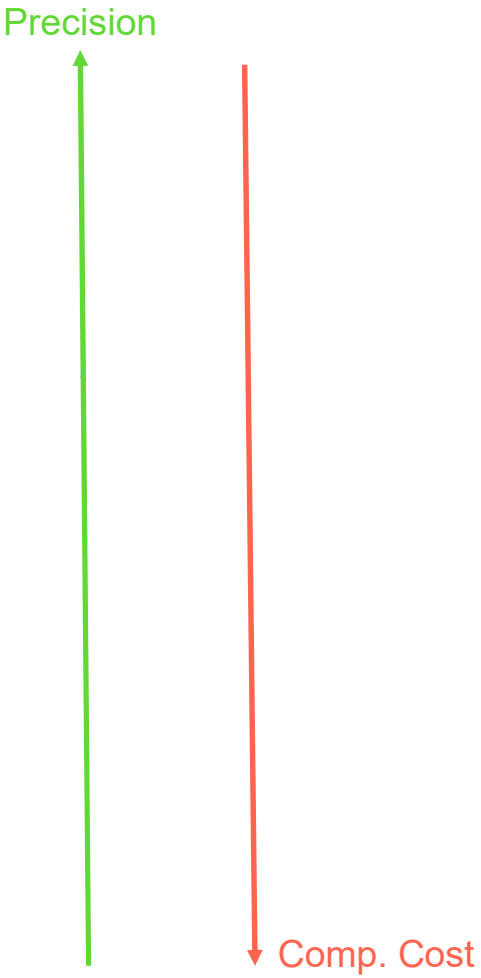
Quantum
- atoms, electrons and electron clouds included
- explicit solvent
- quantum mechanics

All-atom
- all or most atoms present
- explicit solvent
- molecular dynamics

Coarse-grained
- beads comprising a few atoms
- explicit or implicit solvent
- molecular dynamics

Supra-coarse-grained
- interaction sites comprising many atoms, protein parts or proteins
- implicit solvent
- stochastic dynamics

Continuum
- materials as a continuous mass
- implicit solvent
- continuum mechanics



Ingólfsson, Helgi I., et al. "Computational 'microscopy'of cellular membranes." *Journal of cell science* 129.2 (2016): 257-268.

2. Approximations

Approximations

Outline

https://www.chemie-schule.de/KnowHow/Erwin_Schr%C3%B6dinger

1. Born-Oppenheimer
2. Nuclei move classically

Occasionally used in QM

3. Parametrize Force Field

Approximations

1. Born-Oppenheimer

- $m_N \gg m_e$

- $v_N \ll v_e$

Approximations

1. Born-Oppenheimer

$$i\hbar\frac{\partial\Psi(R,r,t)}{\partial t} = -\frac{\hbar^2}{2m}\frac{\partial^2}{\partial r^2}\Psi(R,r,t) - \frac{\hbar^2}{2M}\frac{\partial^2}{\partial R^2}\Psi(R,r,t) + V\Psi(R,r,t)$$

$$\boxed{\Psi(R,r,t) = \psi(R,t)\phi(r)}$$

$$E_e(R)\phi(r) = -\frac{\hbar^2}{2m}\frac{\partial^2}{\partial r^2}\phi(r) + V(R)\phi(r)$$

$$i\hbar\frac{\partial\psi(R)}{\partial t} = -\frac{\hbar^2}{2M}\frac{\partial^2}{\partial R^2}\psi(R,t) + E_e(R)\psi(R,t)$$

Approximations

2. Nuclei move classically

$$i\hbar\frac{\partial\psi(R)}{\partial t} = -\frac{\hbar^2}{2M}\frac{\partial^2}{\partial R^2}\psi(R,t) + E_e(R)\psi(R,t)$$

$$\boxed{\frac{\partial^2 R}{\partial t^2} = -\frac{\nabla_R E_e(R)}{M}}$$

Approximations

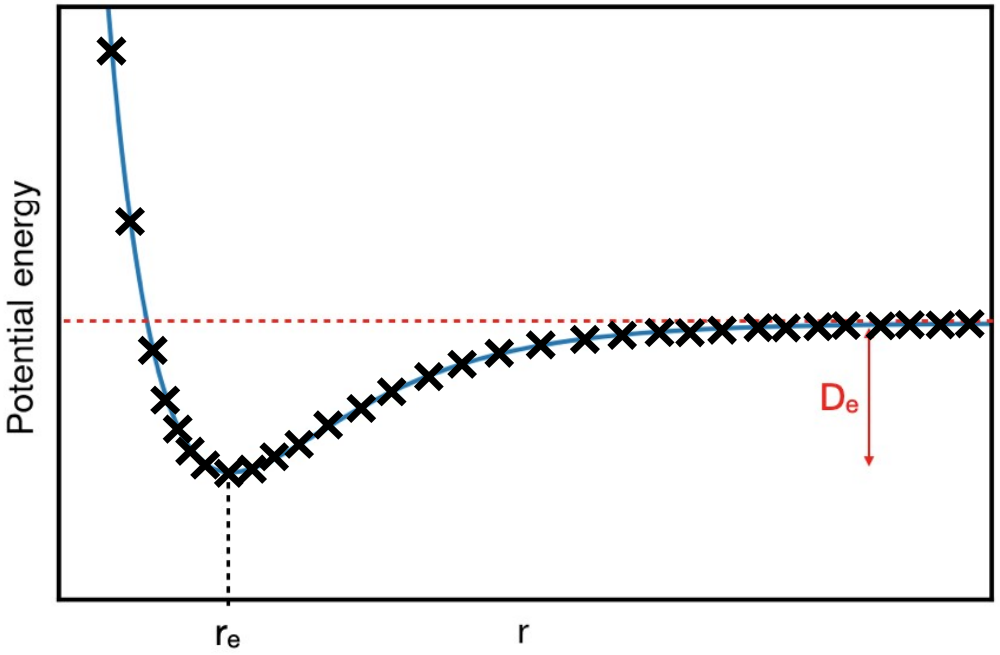
2. Nuclei move classically - Breakdowns:

- Tunneling protons

- Vibrational modes

Approximations

3. Parametrize Force Field



H_2 parameters:

$D_e = 4.75$ eV

$r_e = 0.741$ Å

$a = 1.93$ Å^{-1}

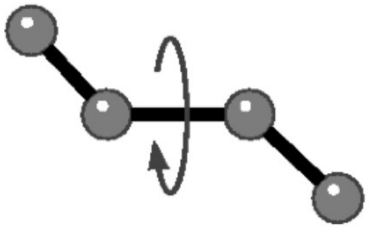
$$V = D_e\left(1-e^{-a(r-r_e)}\right)^2$$

https://chem.libretexts.org/Courses/Western_Washington_University/Biophysical_Chemistry_%28Smirnov_and_McCarty%29/03%3A_Molecular_Mechanics_and_Statistical_Thermodynamics/3.01%3A_Potential_Energy_Surface_and_Bonding_Interactions

3. Force Fields

Force Fields

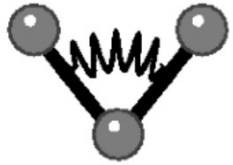
Amber



Bond length

$$E_{total} = \sum_{bonds} k_b(r - r_0)^2$$

Bond angle



$$+ \sum_{angles} k_\theta(\theta - \theta_0)^2$$

Dihedral angles

$$+ \sum_{dihedrals} V_n[1 + \cos(n\phi - \gamma)]$$

Van der Waals forces

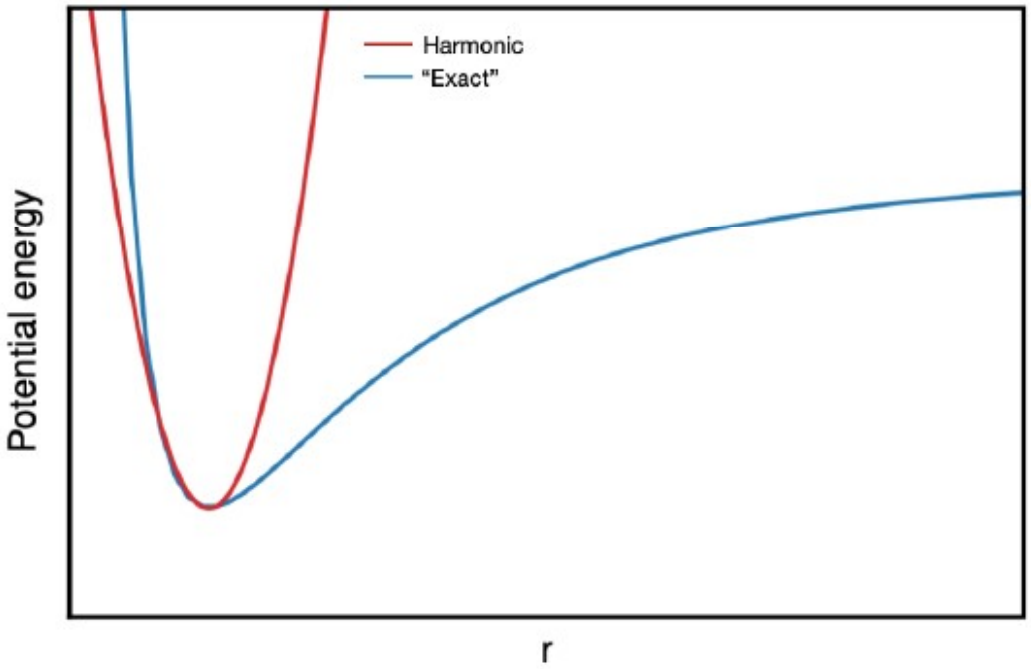
$$+ \sum_{i=1}^{N-1} \sum_{j=i+1}^{N} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}} \right]$$

Electrostatics

https://ambermd.org/doc12/Amber23.pdf#page=276

Force Fields

Harmonic Approximation



https://chem.libretexts.org/Courses/Western_Washington_University/Biophysical_Chemistry_%28Smirnov_and_McCarty%29/03%3A_Molecular_Mechanics_and_Statistical_Thermodynamics/3.01%3A_Potential_Energy_Surface_and_Bonding_Interactions

Force Fields

Chamber

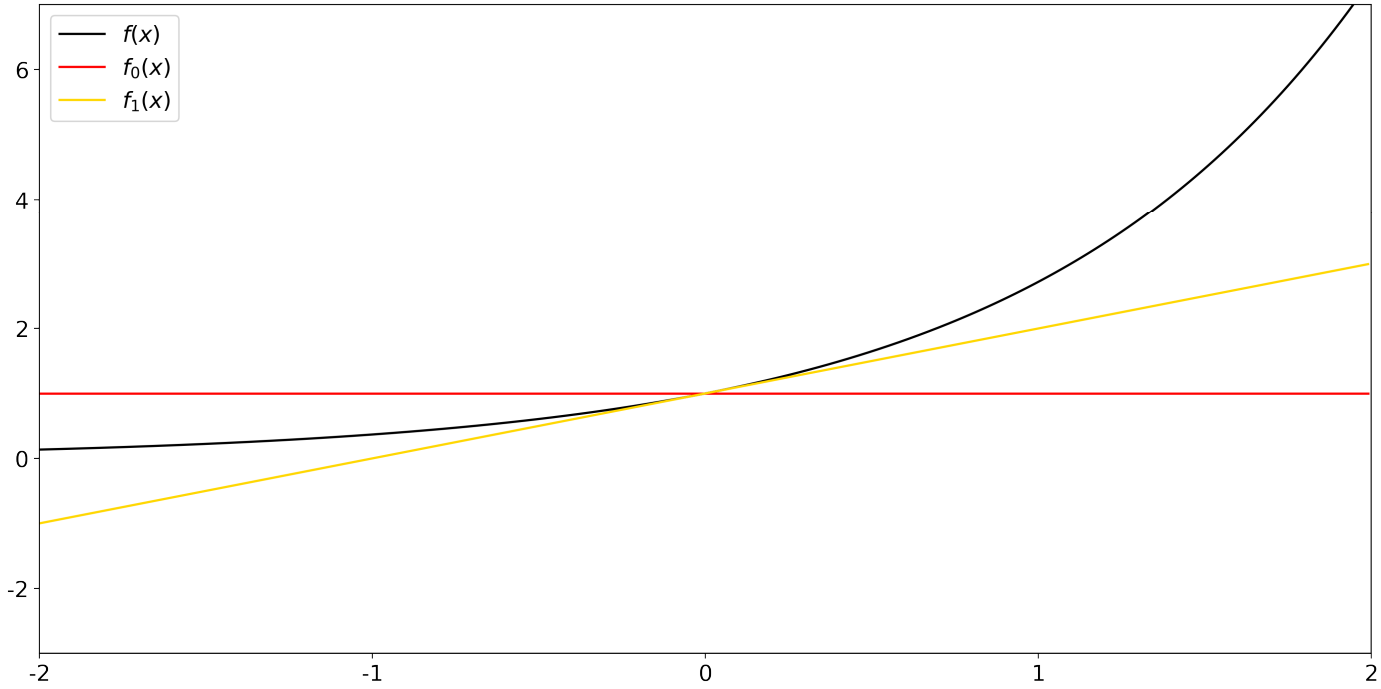
```
ATOMS
MASS    31 H      1.00800 ! polar H
MASS    32 HC     1.00800 ! N-ter H
MASS    33 HA     1.00800 ! nonpolar H
MASS    34 HP     1.00800 ! aromatic H
MASS    35 HB1    1.00800 ! backbone H
MASS    36 HB2    1.00800 ! aliphatic backbone H, to CT2
MASS    37 HR1    1.00800 ! his he1, (+) his HG,HD2
MASS    38 HR2    1.00800 ! (+) his HE1
MASS    39 HR3    1.00800 ! neutral his HG, HD2
MASS    40 HS     1.00800 ! thiol hydrogen
MASS    41 HE1    1.00800 ! for alkene; RHC=CR
MASS    42 HE2    1.00800 ! for alkene; H2C=CR
MASS    43 HA1    1.00800 ! alkane, CH, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS    44 HA2    1.00800 ! alkane, CH2, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS    45 HA3    1.00800 ! alkane, CH3, new LJ params (see toppar_all22_prot_aliphatic_c27.str)
MASS    46 C     12.01100 ! carbonyl C, peptide backbone
MASS    47 CA    12.01100 ! aromatic C
MASS    48 CT    12.01100 ! aliphatic sp3 C, new LJ params, no hydrogens, see retinol stream file for parameters
MASS    49 CT1   12.01100 ! aliphatic sp3 C for CH
MASS    50 CT2   12.01100 ! aliphatic sp3 C for CH2
MASS    51 CT2A  12.01100 ! from CT2 (GLU, HSP chi1/chi2 fitting) 05282010, zhu
MASS    52 CT3   12.01100 ! aliphatic sp3 C for CH3
MASS    53 CPH1  12.01100 ! his CG and CD2 carbons
MASS    54 CPH2  12.01100 ! his CE1 carbon
```

4. Algorithms

Algorithms

Repetition – Taylor Series

$$f(x) = \sum_{i=0}^{\infty} \frac{f^{(i)}(x_0)}{i!}(x - x_0)^i$$

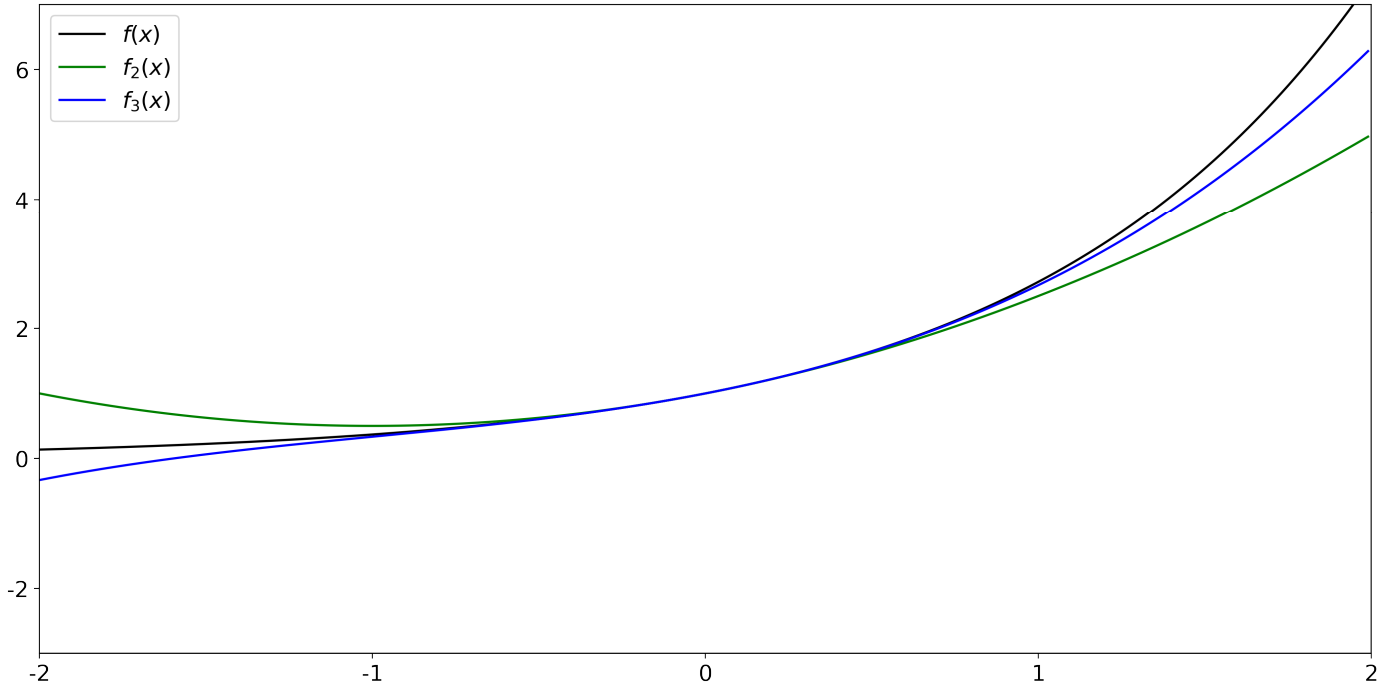


$$f(x) = e^x$$
$$f_0(x) \approx 1$$
$$f_1(x) \approx 1 + x$$

Algorithms

Repetition – Taylor Series

$$f(x) = \sum_{i=0}^{\infty} \frac{f^{(i)}(x_0)}{i!}(x - x_0)^i$$



$$f(x) = e^x$$

$$f_0(x) \approx 1$$

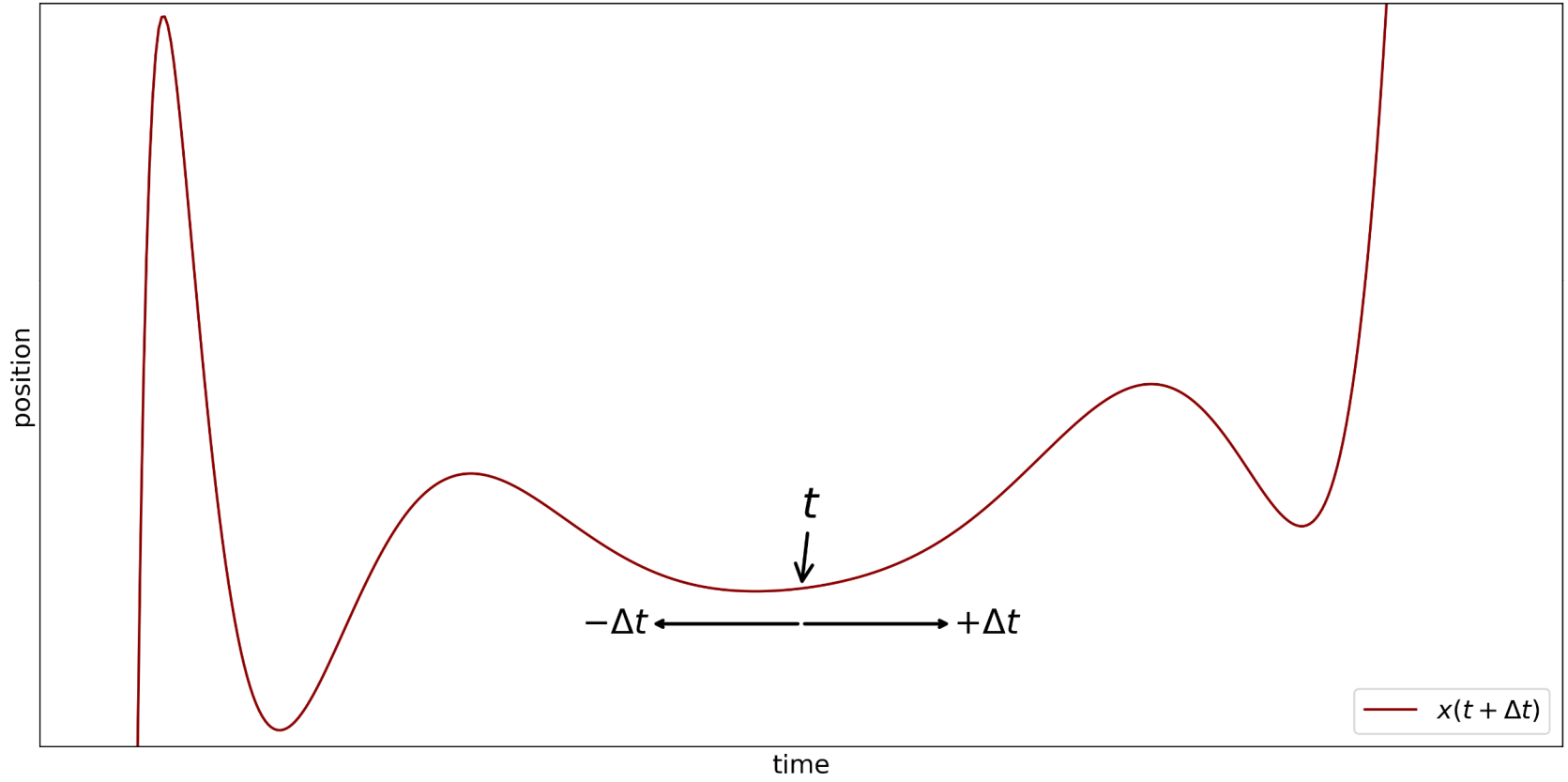
$$f_1(x) \approx 1 + x$$

$$f_2(x) \approx 1 + x + \frac{x^2}{2}$$

$$f_3(x) \approx 1 + x + \frac{x^2}{2} + \frac{x^3}{6}$$

Algorithms

Verlet Algorithm



Algorithms

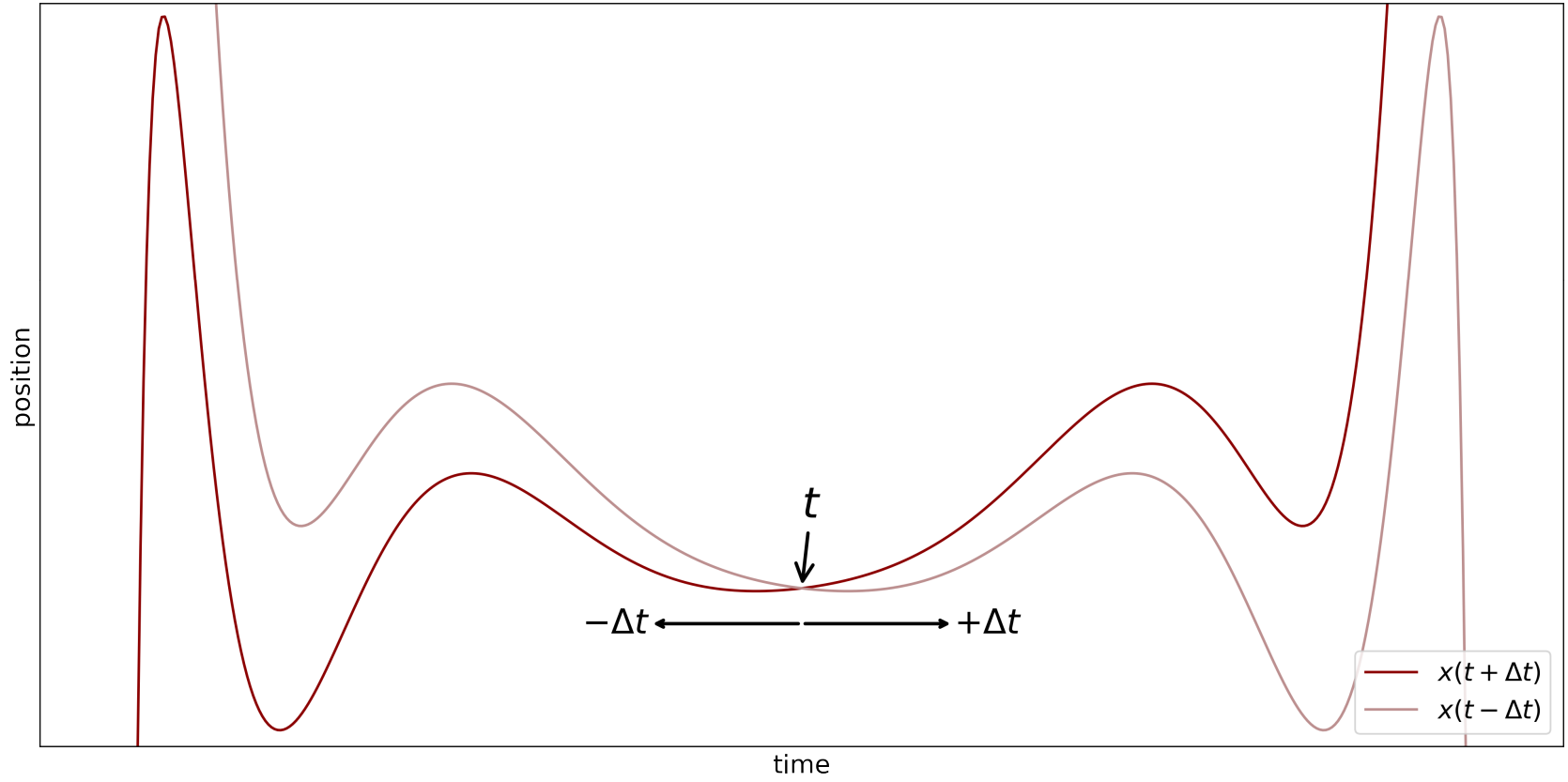
Verlet Algorithm

$$x(t+\Delta t) \approx x(t) + x'(t) \quad \Delta t \quad + \frac{x''(t)}{2} \quad \Delta t^2 \quad + \frac{x'''(t)}{6} \quad \Delta t^3 \quad + \mathcal{O}^4$$

$$x(t-\Delta t) \approx x(t) + x'(t)(-\Delta t) + \frac{x''(t)}{2}(-\Delta t)^2 + \frac{x'''(t)}{6}(-\Delta t)^3 + \mathcal{O}^4$$

Algorithms

Verlet Algorithm



Algorithms

Verlet Algorithm

$$x(t+\Delta t) \approx x(t) + x'(t)\quad \Delta t \quad + \frac{x''(t)}{2}\quad \Delta t^2 \quad + \frac{x'''(t)}{6}\quad \Delta t^3 \quad + \mathcal{O}^4$$

$$x(t-\Delta t) \approx x(t) + x'(t)(-\Delta t) + \frac{x''(t)}{2}(-\Delta t)^2 + \frac{x'''(t)}{6}(-\Delta t)^3 + \mathcal{O}^4$$

$$x(t-\Delta t) \approx x(t) - x'(t)\Delta t + \frac{x''(t)}{2}\Delta t^2 - \frac{x'''(t)}{6}\Delta t^3 + \mathcal{O}^4$$

Algorithms

Verlet Algorithm

$$x(t+\Delta t) \approx x(t) + x'(t)\Delta t + \frac{x''(t)}{2}\Delta t^2 + \frac{x'''(t)}{6}\Delta t^3 + \mathcal{O}^4$$

$$x(t-\Delta t) \approx x(t) - x'(t)\Delta t + \frac{x''(t)}{2}\Delta t^2 - \frac{x'''(t)}{6}\Delta t^3 + \mathcal{O}^4$$

$$x(t+\Delta t) + x(t-\Delta t) \approx 2x(t) \qquad + x''(t)\Delta t^2 \qquad + \mathcal{O}^4$$

Algorithms

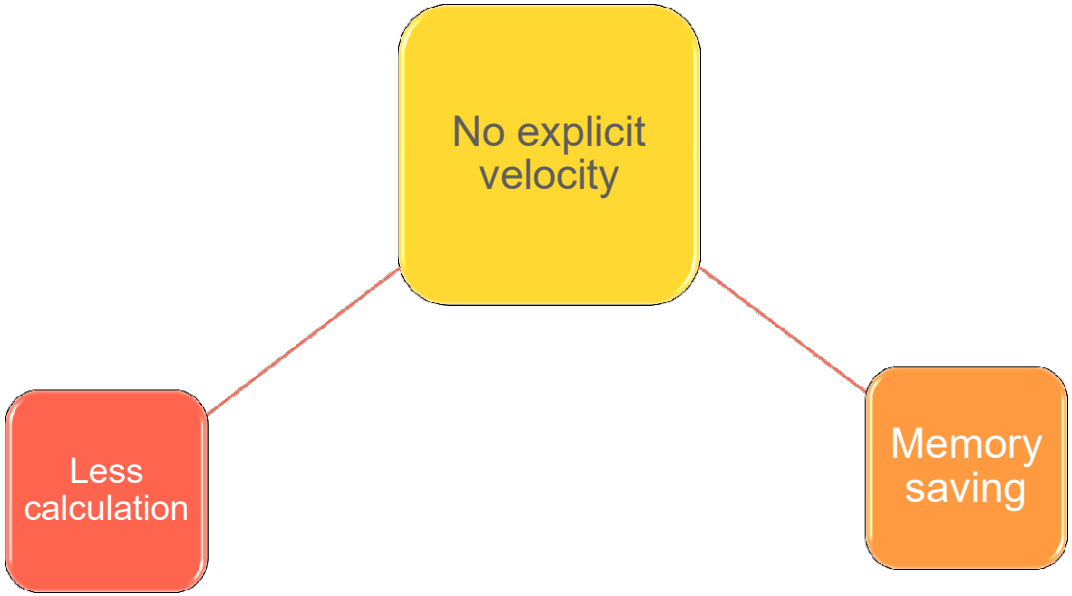
Verlet Algorithm

Correct up to 3rd order!

$$x(t+\Delta t) \approx 2x(t) - x(t-\Delta t) + x''(t)\Delta t^2 + \mathcal{O}^4$$

Algorithms

Verlet Algorithm - Advantages



5. Coarse Grained Simulation

Coarse Grained Simulations

Outline

1. Simple Coarse Graining
2. Brownian Dynamics
3. Implicit Solvents

Coarse Grained Simulations

Important Models

- Martini
- Sirah

Coarse Grained Simulations

Sirah

http://www.sirahff.com/2012/06/sirah-forcefield.html

Coarse Grained Simulations

Brownian Dynamics

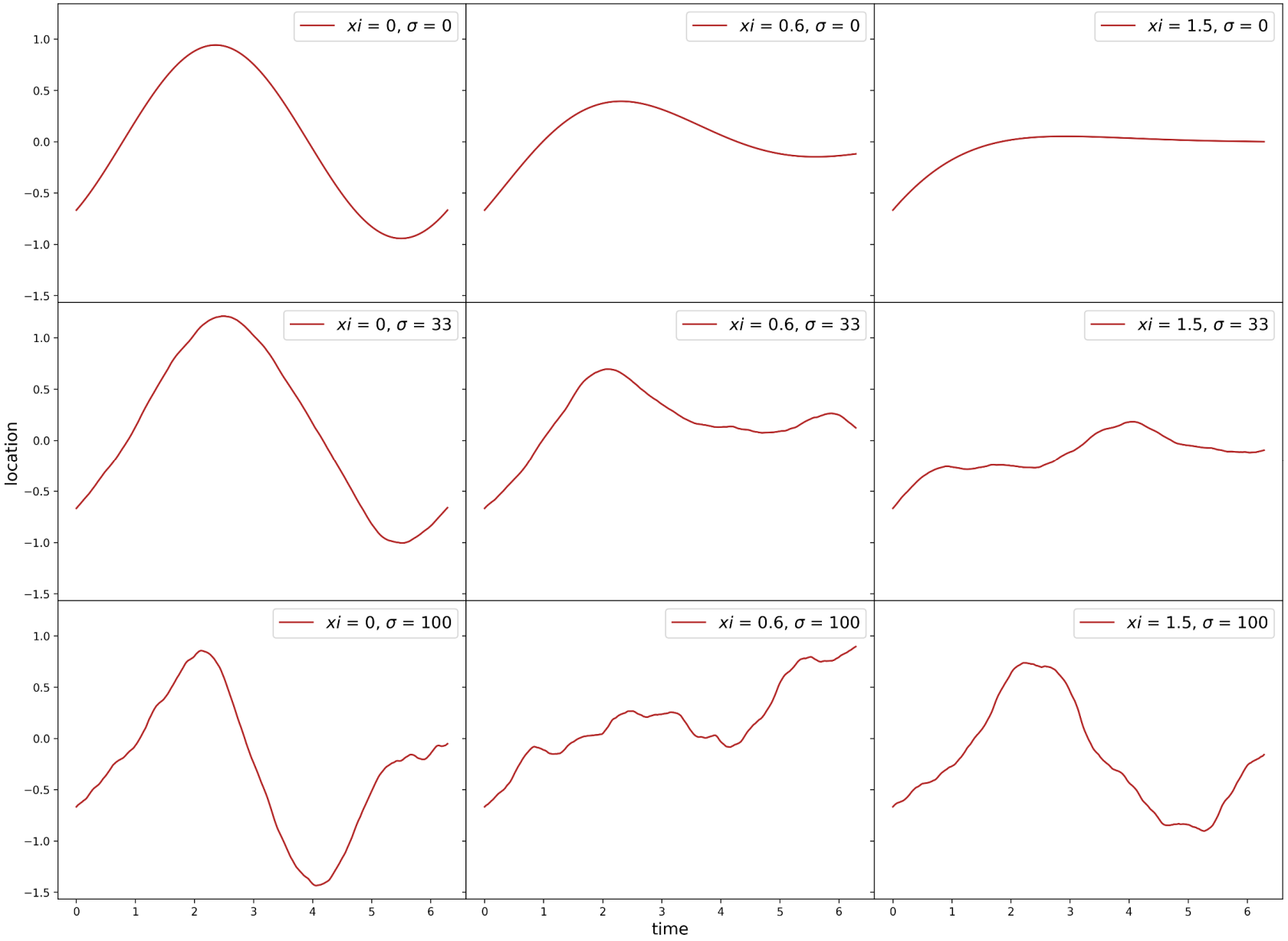
$$m\dot{v} = -\nabla V - \xi v(t) + \sigma\eta(t)$$

- ξ : Stokes friction
- σ : Random Force Amplitude
- $\eta(t)$: Random Force

Coarse Grained Simulations

Brownian Dynamics

$$m\dot{v} = -\nabla V$$
$$-\xi v(t) + \sigma\eta(t)$$



Coarse Grained Simulations

Implicit Solvents

$$\Delta G_{solv} = \sum_i \sigma_i ASA_i$$

- σ_i : Free energy interaction - „Surface Tension“

- ASA_i : Accesible Solvent Area

6. Recipe

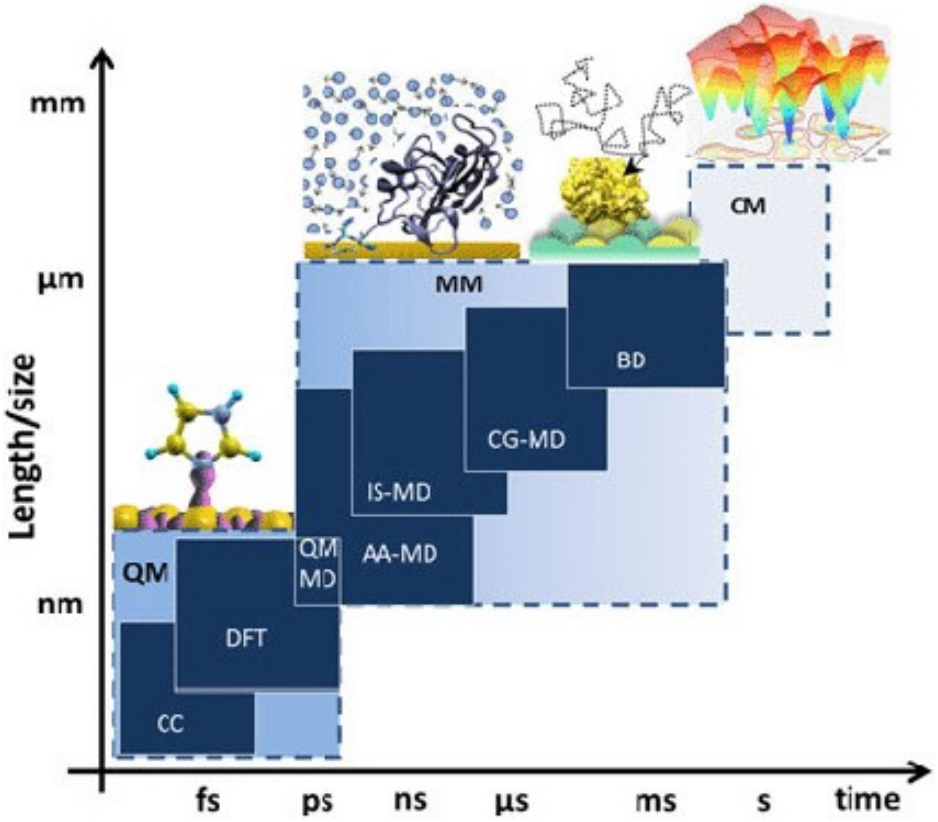
Recipe

Overview

1. Making Decisions
2. Data preparation
3. Minimization
4. Equilibration
5. Simulation

Recipe

1. Which model?



Tunneling protons?

Chemical reactions?

Recipe

1. Which software?

HOOMD blue

AMBER MD

CHARMM
Chemistry at HARvard Macromolecular Mechanics

LAMMPS

NAMD
Scalable Molecular Dynamics

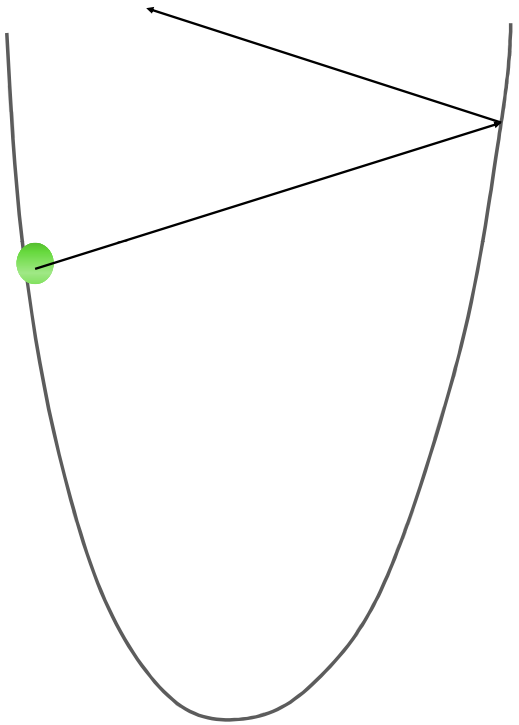
Recipe

2. Data preparation

- .pdb file clean?
- add water
- add ions

Recipe

3. Minimization



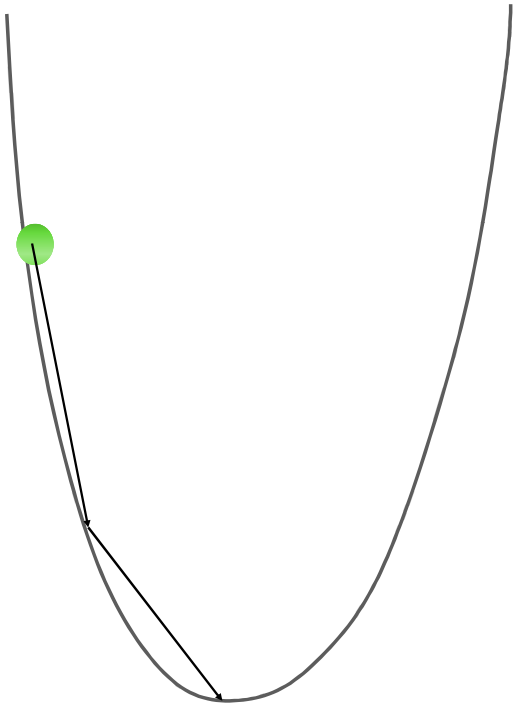
$$x''(t)\Delta t^2$$

$$\downarrow$$

$$\nabla V = x'' \text{ too big}$$

Recipe

3. Minimization

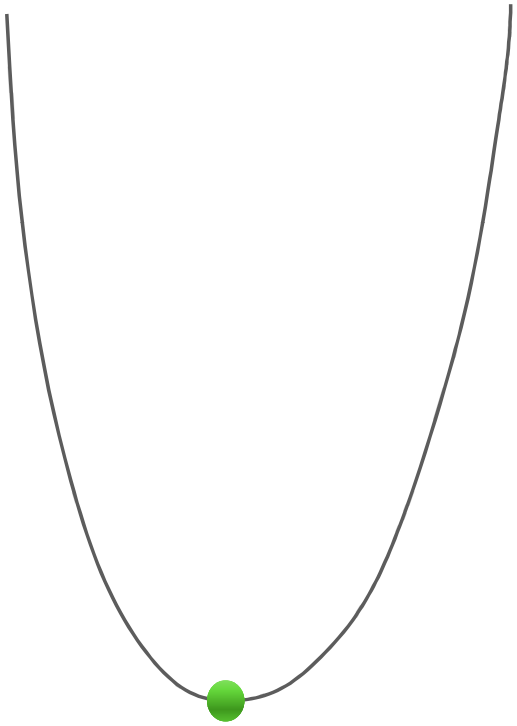


$$x''(t)\Delta t^2$$

Δt very small

Recipe

4. Equilibration



$T = ?$

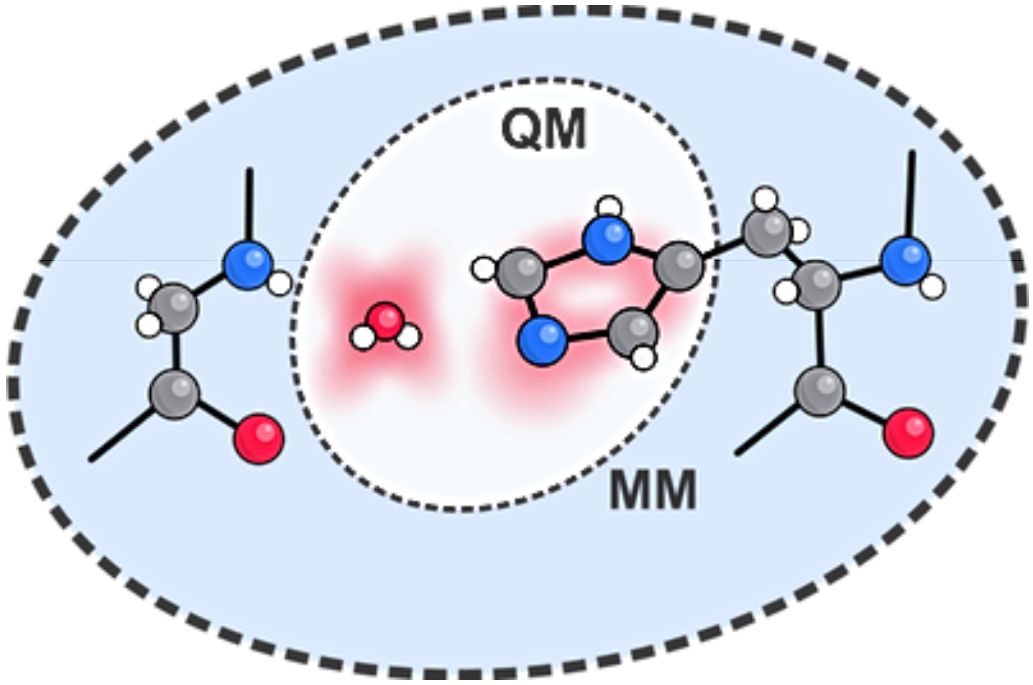
Recipe

5. Simulation

7. Further Studying and Possibilities

Further Studying

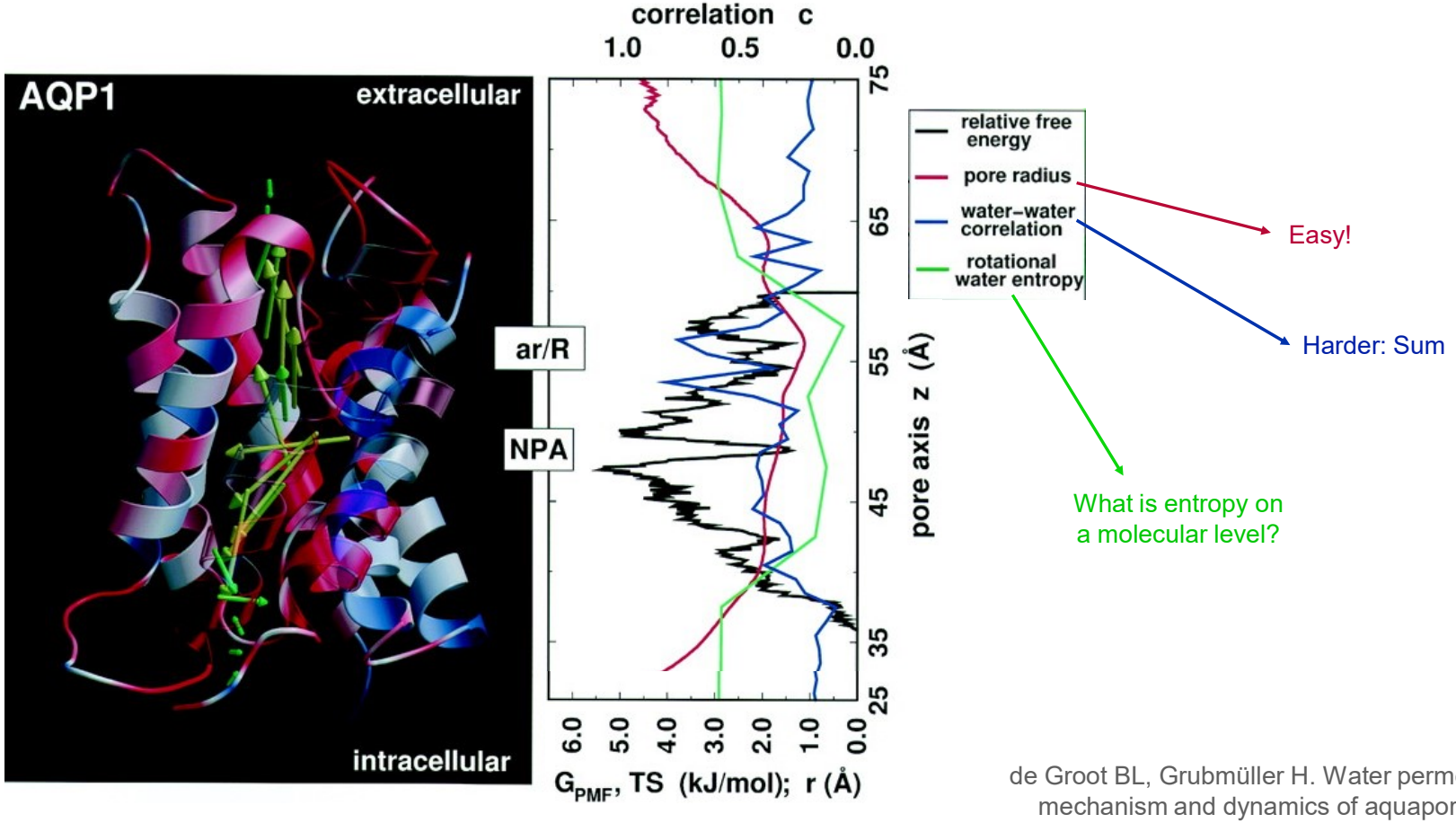
QM / MM



https://www.hzdr.de/db/PicUser?pOid=67411

Further Studying

How do we extract information from Simulations?



de Groot BL, Grubmüller H. Water permeation across biological membranes: mechanism and dynamics of aquaporin-1 and GlpF. Science. 2001 Dec 14;294(5550):2353-7. doi: 10.1126/science.1066115. PMID: 11743202.

Further Studying

How do we manage other parameters?

- Thermostats / Barostats
- Fast Electrostatics (Ewald Summation)
- NMA/PCA

Further Studying

Helpful Courses

- Theoretical Chemistry 1 / 2
- Numerics
- Theoretical Statistical Physics

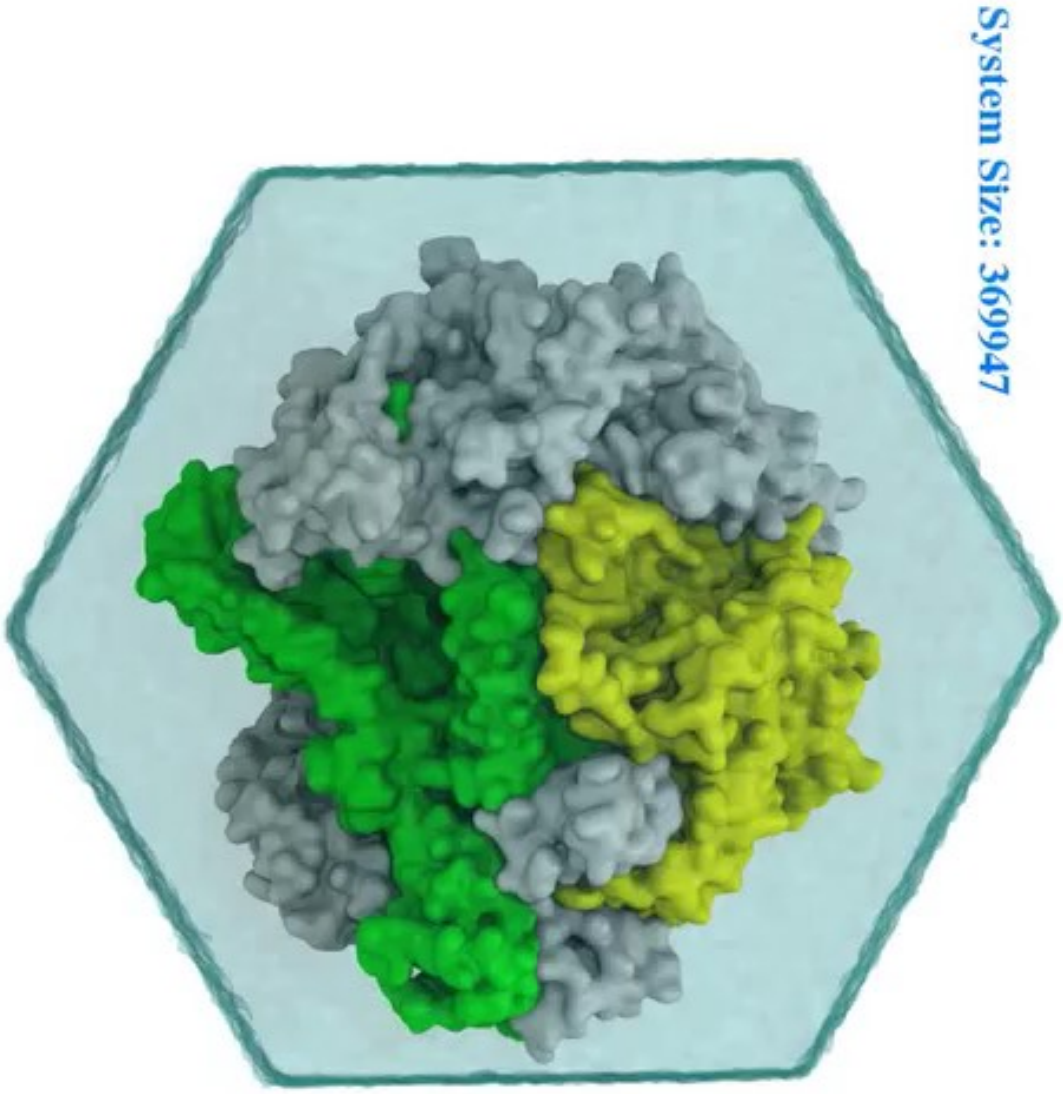
Possibilities

Examples

- DNA Polymerase
- Cytoplasm
- Enzyme Catalysis

Possibilities

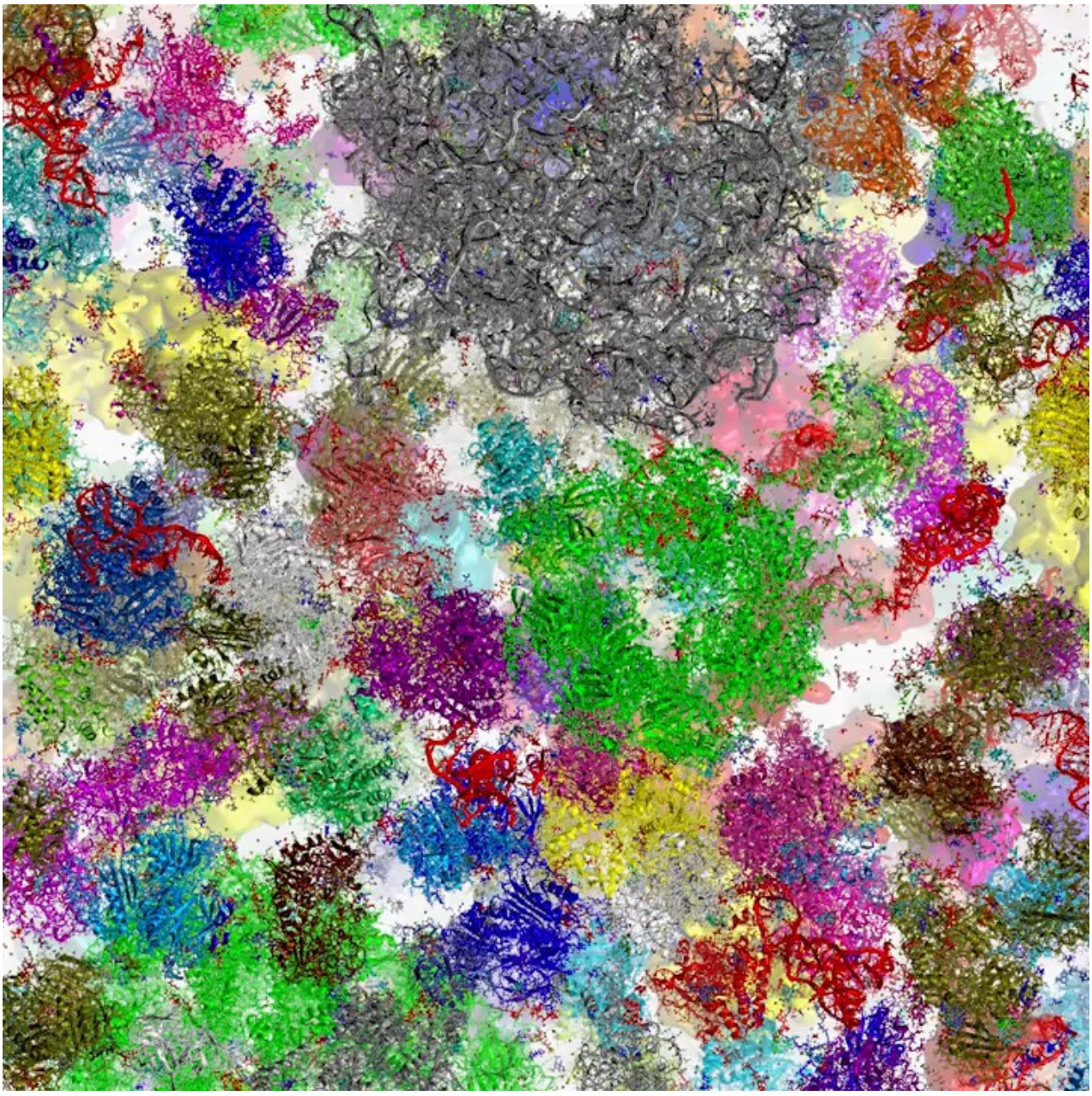
DNA Polymerase



Da, LT., Pardo-Avila, F., Xu, L. *et al.* Bridge helix bending promotes RNA polymerase II backtracking through a critical and conserved threonine residue. *Nat Commun* **7**, 11244 (2016). https://doi.org/10.1038/ncomms11244

Possibilities

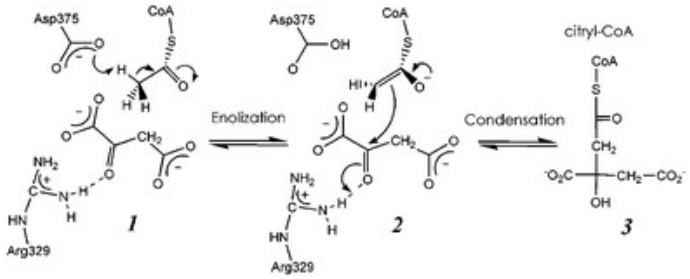
Cytoplasm



Isseki Yu, Takaharu Mori, Tadashi Ando, Ryuhei Harada, Jaewoon Jung, Yuji Sugita, Michael Feig (2016) Biomolecular interactions modulate macromolecular structure and dynamics in atomistic model of a bacterial cytoplasm eLife 5:e19274 https://doi.org/

Possibilities

Citrate Synthase



COMMUNICATION www.rsc.org/chemcomm | ChemComm

High-level QM/MM modelling predicts an arginine as the acid in the condensation reaction catalysed by citrate synthase†

Marc W. van der Kamp,[a] Francesca Perruccio[ab] and Adrian J. Mulholland*[a]

Received (in Cambridge, UK) 21st January 2008, Accepted 25th February 2008
First published as an Advance Article on the web 11th March 2008
DOI: 10.1039/b800496j

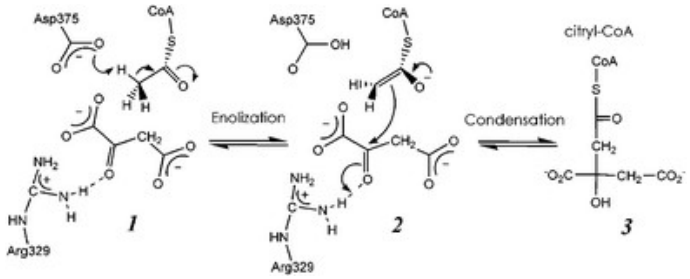
High-level *ab initio* quantum mechanical/molecular mechanical (QM/MM) modelling of citryl-CoA formation in citrate synthase reveals that an arginine residue acts as the proton donor; this proposed new mechanism helps to explain how chemical and large scale conformational changes are coupled in this paradigmatic enzyme.

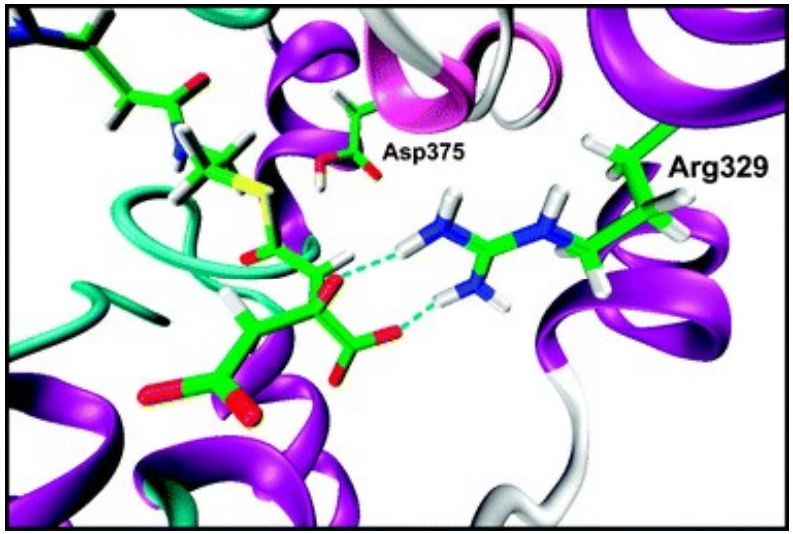
Here, we report the first modelling of the condensation reaction in CS, using high level *ab initio* QM/MM methods. The calculated potential energy profile shows that Arg329 can act as the proton donor, leading to a stable citryl-CoA intermediate. After proton abstraction from acetyl-CoA, carbon–carbon bond formation starts first but is concerted with

Van der Kamp, M. W., Perruccio, F., and Mulholland, A. J. (**2008**) High-level QM/MM modelling predicts an arginine as the acid in the condensation reaction catalysed by citrate synthase Chem. Commun. 1874– 1876

Possibilities

Citrate Synthase





Van der Kamp, M. W., Perruccio, F., and Mulholland, A. J. (**2008**) High-level QM/MM modelling predicts an arginine as the acid in the condensation reaction catalysed by citrate synthase Chem. Commun. 1874– 1876

Takeaway

1. Scale method to problem
2. Force fields parametrize QM interactions
3. Force fields have 5 different contributions
4. Verlet is 3rd order algorithm
5. Simulations rely on fundamental physics

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MAX PLANCK SCHOOL matter to life

Profile

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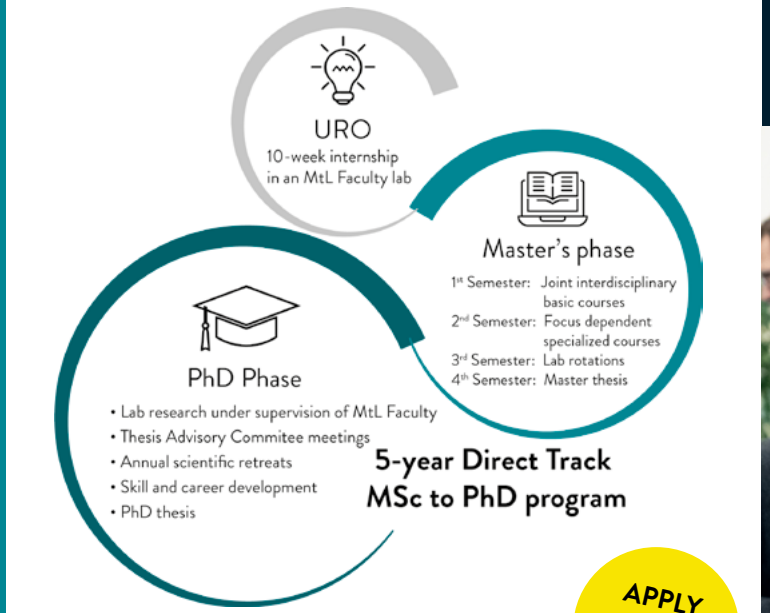
„What is Life"?



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The Master's phase includes lecture modules, lab rotations, internships, and the master thesis, thus giving you a theoretical and practical overview of the research done by our faculty. These experiences will perfectly prepare you to make an informed decision regarding the lab and project in which to carry out your PhD thesis in.

Continuous support in the form of mentoring by peers & faculty, thesis advisory committee meetings, funding for travelling to conferences and career trainings are also provided.

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Candidates with a Bachelor's degree (B.Sc or B.E) or who are in their final study year in chemistry, biochemistry, physics, bioengineering or related subjects. And of course, passion for science and research!

"The program offers a truly interdisciplinary education. I am able to take classes in a variety of fields and connect with international students and faculty from different backgrounds. The professors are knowledgeable and supportive. I particularly appreciate the hands-on learning opportunities at the University and Max Planck Institute for Medical Research with top-notch facilities."

Deus Mwesigwa, 24, Matter to Life, Master Student

FIND OUT MORE

Important dates

September 1 - Start of application phase

December 1 - Application deadline

September 1 (following year) - Program start

Join one of our online info sessions!

Find the dates on our website during the application phase

Check our website for more information

Master/PhD Program

https://mattertolife.maxplanckschools.org/program

MtL URO Program

mattertolife.maxplanckschools.org/uro-research-internship

Contact us

mattertolife@maxplanckschools.de

uro@mtl.maxplanckschools.de

Follow us on Social Media

MTL URO PROGRAM

Undergraduate Research Opportunities

The Matter to Life school offers outstanding undergraduate students the opportunity to expand their research experience through our Undergraduate Research Opportunities (URO) program.

Who can apply?

All motivated undergraduate students during their Bachelor studies in an MtL related field are eligible to apply!

What the MtL URO program entails

- A 10-week hands on internship in one of the laboratories of our renowned faculty
- Learn cutting-edge scientific methods in the context of Matter to Life
- Gain insights into the Matter to Life community
- Establish your network and expand your knowledge in an highly interdisciplinary field
- Receive financial support for your travel, accommodation and living expenses during your stay