Testing for Physical Validity in Molecular Simulations

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Reproducibility of Molecular Modeling and Simulation Workshop
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Acknowledgements

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You?

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Turning Discovery Into Health

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Outline

- Some physical assumptions and their validation
- Python module **`physical-validation`**
- PEBCAK
- Outlook & Conclusion

Downloads for tutorials

- Git clone data from:
- `https://github.com/shirtsgroup/physical_validation_workshop`
- OR download from: http://bit.ly/2LhjrEj
- ALSO run:
- `pip install physical_validation`
- (may need to do `pip install numpy scipy matplotlib`)

Physically correct simulations are necessary for reproducibility

Correct simulations

incorrect simulation

"~~Happy families~~ are all alike; every ~~unhappy family~~ is ~~unhappy~~ in its own way."

incorrect

- Leo Tolstoy, first line of *Anna Karenina*

Physically correct simulations are necessary for reproducibility

Correct simulations are all alike; every incorrect simulation is incorrect in its own way

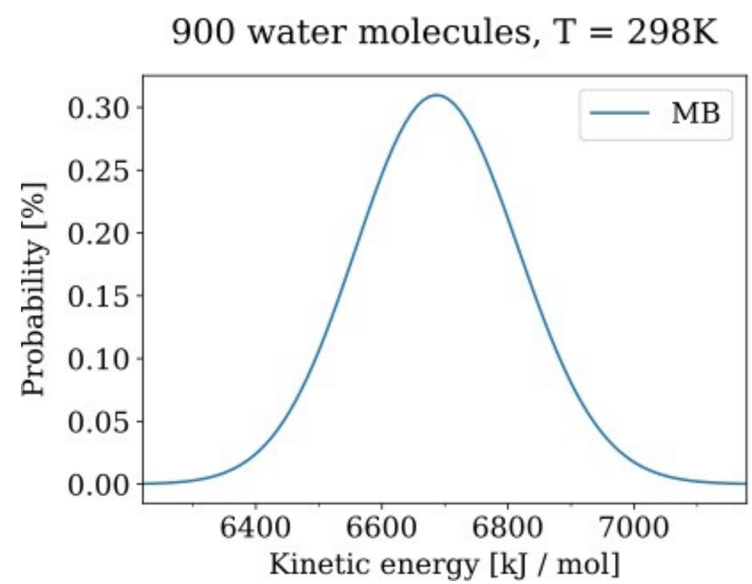
- There are many ways to not conserve energy
- There are many ways to not have equipartition of energy
- There are many ways to not be Boltzmann weighted
- There are many ways to create a steady state

Test: Is the kinetic energy Maxwell-Boltzmann distributed?

- *Expectation:* Kinetic energy K is Maxwell-Boltzmann (MB) distributed:

$$P(K) \propto K^{\frac{N-2}{2}} e^{-\beta K}$$

- MB distribution is a χ^2 distribution → statistical tests available (*e.g.* Kolmogorov-Smirnov test)
- K is a trajectory / distribution
- Null hypothesis:
  K is MB distributed
- Given confidence level α, what is the probability the null hypothesis is violated?



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Test: Is the kinetic energy Maxwell-Boltzmann distributed?

- *Expectation:* Kinetic energy K is Maxwell-Boltzmann (MB) distributed:

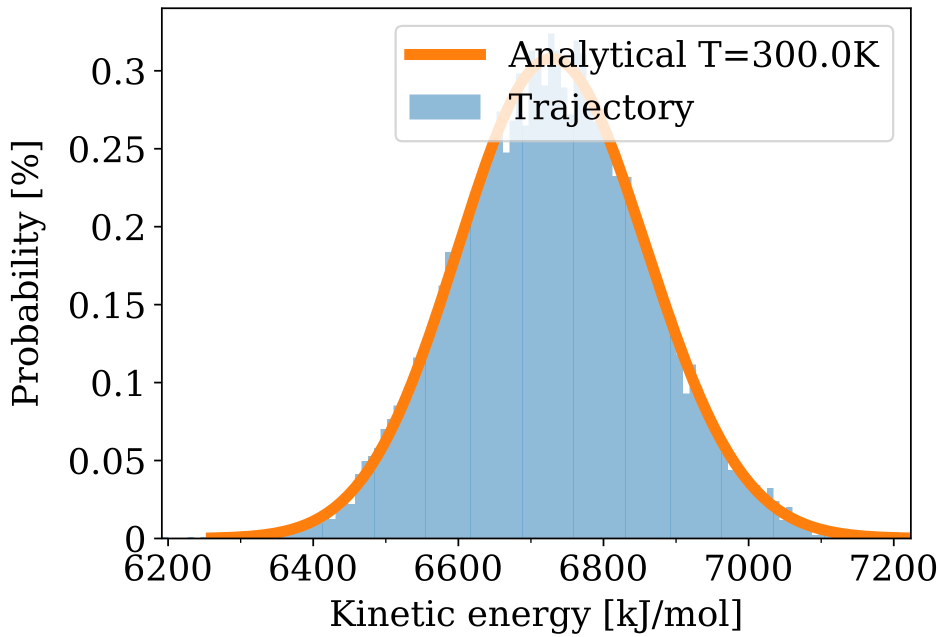
$$P(K) \propto K^{\frac{N-2}{2}} e^{-\beta K}$$

Simpler test, that can be less dependent on noise
Average KE must be 1/2 $k_B T$ x [# degrees of freedom]
Variance of KE must be: 1/2 $(k_B T)^2$ x [# degrees of freedom]

A given distribution of <u>observed</u> kinetic energy implies two temperatures: T_μ and T_σ
Are these both consistent with $T_{\text{what I meant to run}}$?

Example: Kinetic energy distributions

Velocity rescale thermostat

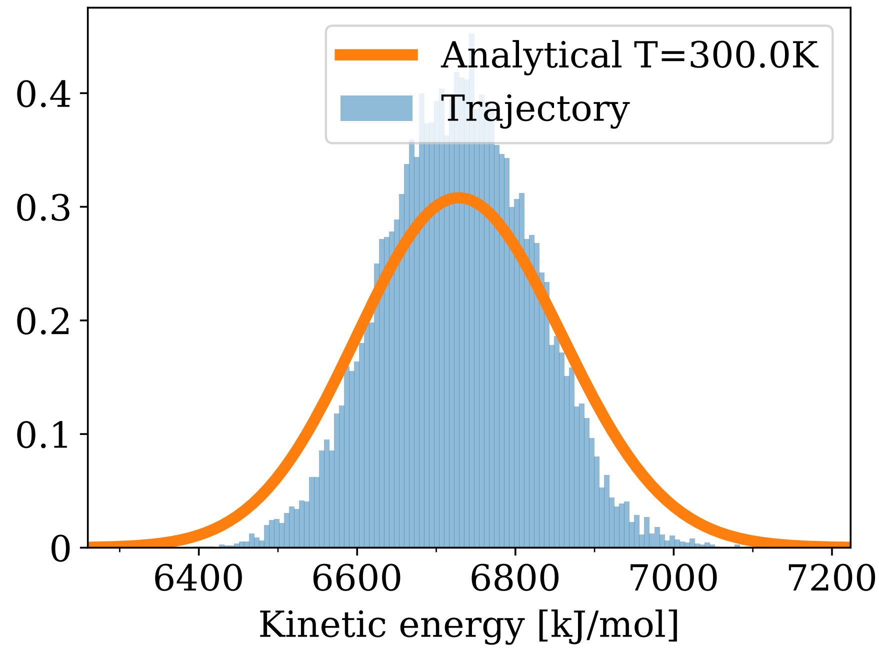


$T_\mu = 299.94 \pm 0.04$ K

$T_\sigma = 301.01 \pm 1.47$ K

$p = 0.214045$

Berendsen thermostat



$T_\mu = 299.99 \pm 0.03$ K

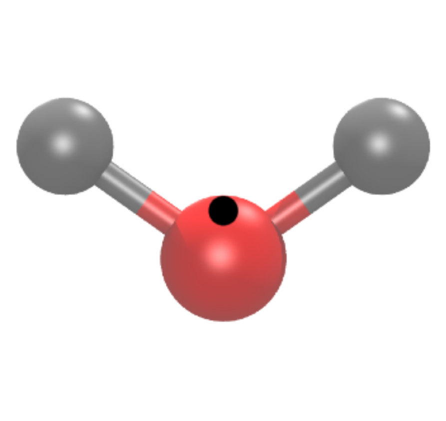
$T_\sigma = 222.60 \pm 1.16$ K

$p = 8.42116 \times 10^{-83}$

Test: Does equipartition hold for the kinetic energy?

Equipartition expected – homogeneous temperature!

- Parts of the system:
  Functional / arbitrary divisions
  - Randomly divide molecules in groups
  - Compare solute / solvent temperatures
  - Compare temperatures of components of liquid mixture
- Sets of degrees of freedom (DoF)
  Rigid body / internal DoF



Jellinek & Li, Phys Rev Lett (1989)

Test: Is the expected statistical-mechanical ensemble (NVT / NPT / μVT) sampled?

Run the same system, same options,
except at two different temperatures

$$P_1(E) = Q_1^{-1}\Omega(E)e^{-\beta_1 E}$$

$$P_2(E) = Q_2^{-1}\Omega(E)e^{-\beta_2 E}$$

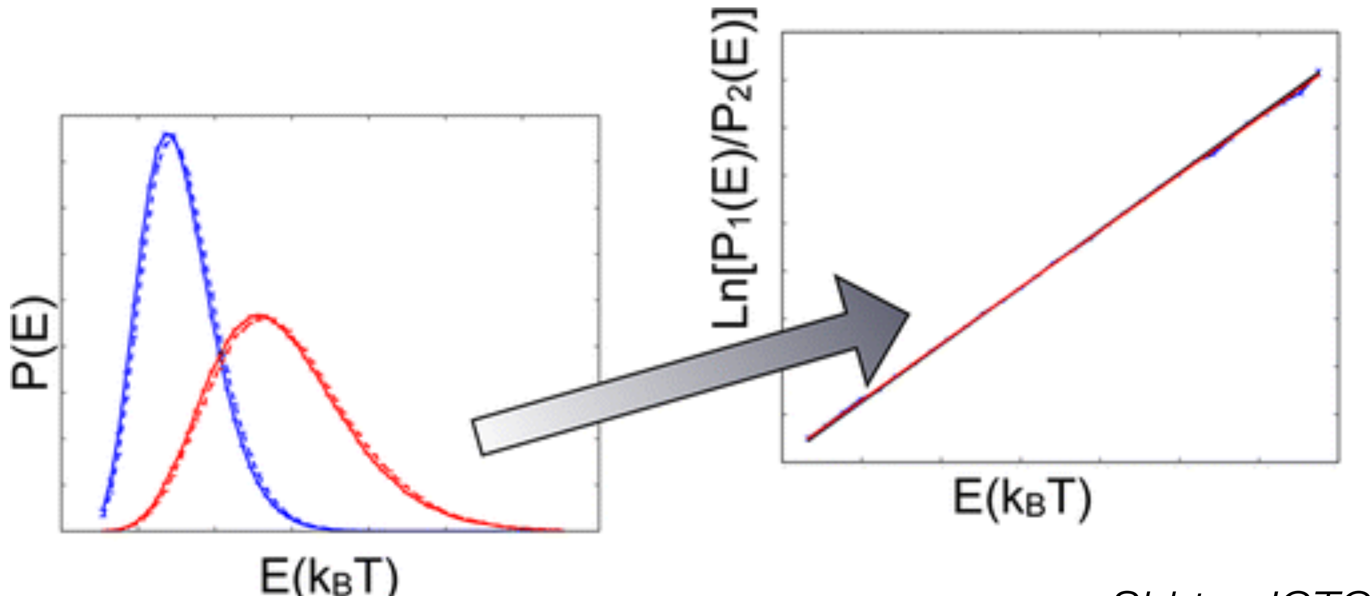
$$\frac{P_1(E)}{P_2(E)} = \frac{Q_2}{Q_1}e^{(\beta_2-\beta_1)E}$$

$$\ln\frac{P_1(E)}{P_2(E)} = \ln\frac{Q_2}{Q_1} + (\beta_2 - \beta_1)E$$

Is the expected statistical-mechanical ensemble (NVT / NPT / μVT) sampled?

- *Unknown:* Analytical distribution of potential energy U, volume V, and/or chemical potential μ

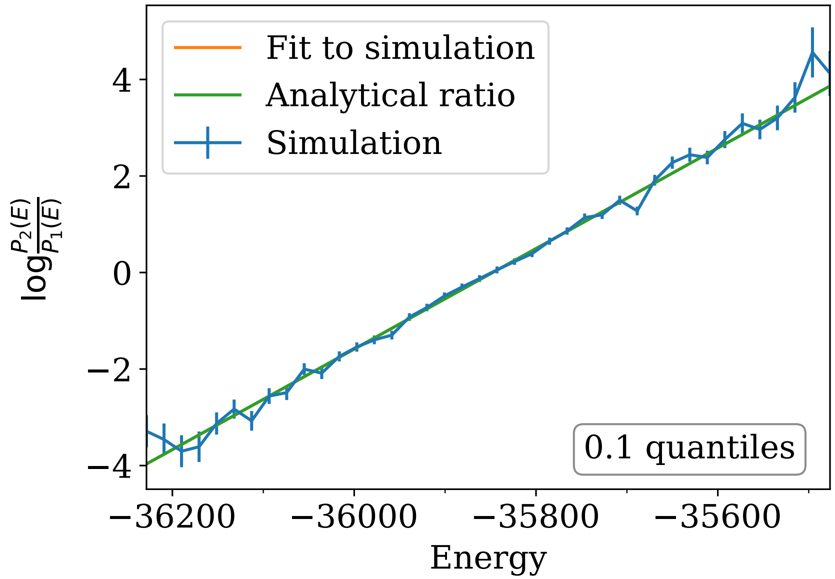
  Known: Ratio of these distributions between two state points (T, P, μ)



Shirts, JCTC (2013)

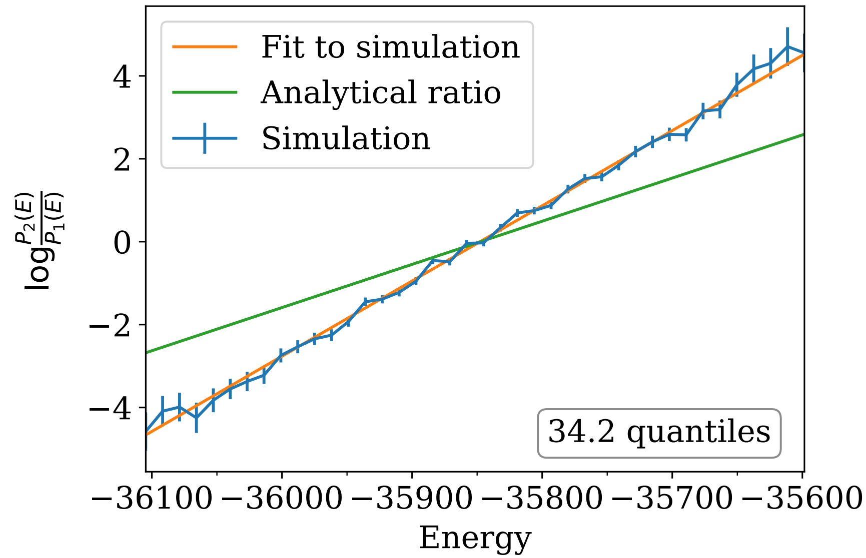
Example: ensemble checking of water potential energy

Velocity rescale thermostat



Analytical: $\beta_1/\beta_2 = 0.010413$
Slope of $P_1(E)/P_2(E) = 0.010420 \pm 0.000127$

Berendsen thermostat



Analytical: $\beta_1/\beta_2 = 0.010413$
Slope of $P_1(E)/P_2(E) = 0.01815 \pm 0.00023$

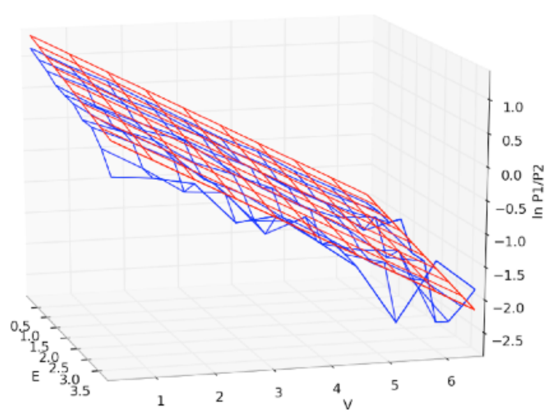
Most thermodynamic ensembles can be checked

- NVT → Fixed ratio of U distributions at two T's
- NPT → Fixed ratio of V distributions at two P's

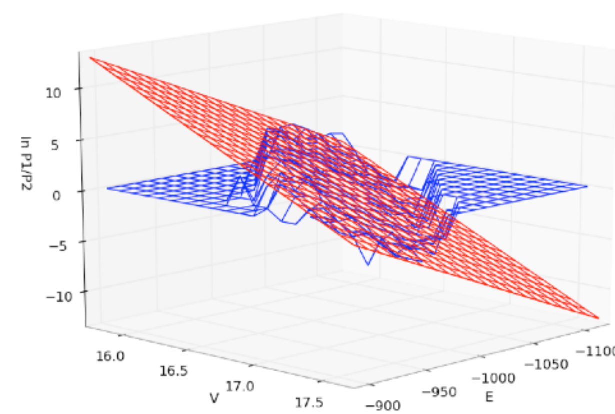
  Fixed ratio of U+PV at two T's

  Fixed plane of U,V joint distribution at pairs of T, P

Ratio of
$P_1(U,V)/P_2(U,V)$



Model with K(V)



Lennard-Jones fluid

Blue = Data
Red = Fit

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Monte Carlo can be checked

- Potential energy and kinetic energy are separable
- So formula is still valid if E = V, instead of E=U

$$\ln \frac{P_1(E)}{P_2(E)} = \ln \frac{Q_2}{Q_1} + (\beta_2 - \beta_1)E$$

Grand canonical and semigrand canonical ensembles can also use the same theory

- $\mu VT \rightarrow$ Fixed ratio of N distributions at two μ's
  Fixed ratio of $U - \mu N$ at two T's
  Fixed plane of (N,μ) joint distribution at pairs of T,μ
- $\Delta\mu VP \rightarrow$ Fixed ratio of N_1 distributions at two Δμ's
  Fixed ratio of $U - \Delta\mu N_1$ at two T's
  Fixed plane of (U, N_1) joint distribution at pairs of T,Δμ

Support for grand and emigrant canonical still in process in current version, but if you want to get it working let us know

Test: Is my integrator doing what I think it is?

- Symplectic NVE integrators do not sample the true Hamiltonian, but a related "shadow Hamiltonian"

$$H = \tilde{H} + \mathcal{O}(\Delta t^2)$$

- Fluctuation δE of constant of motion H(x) = E depend on time step ΔE of integration

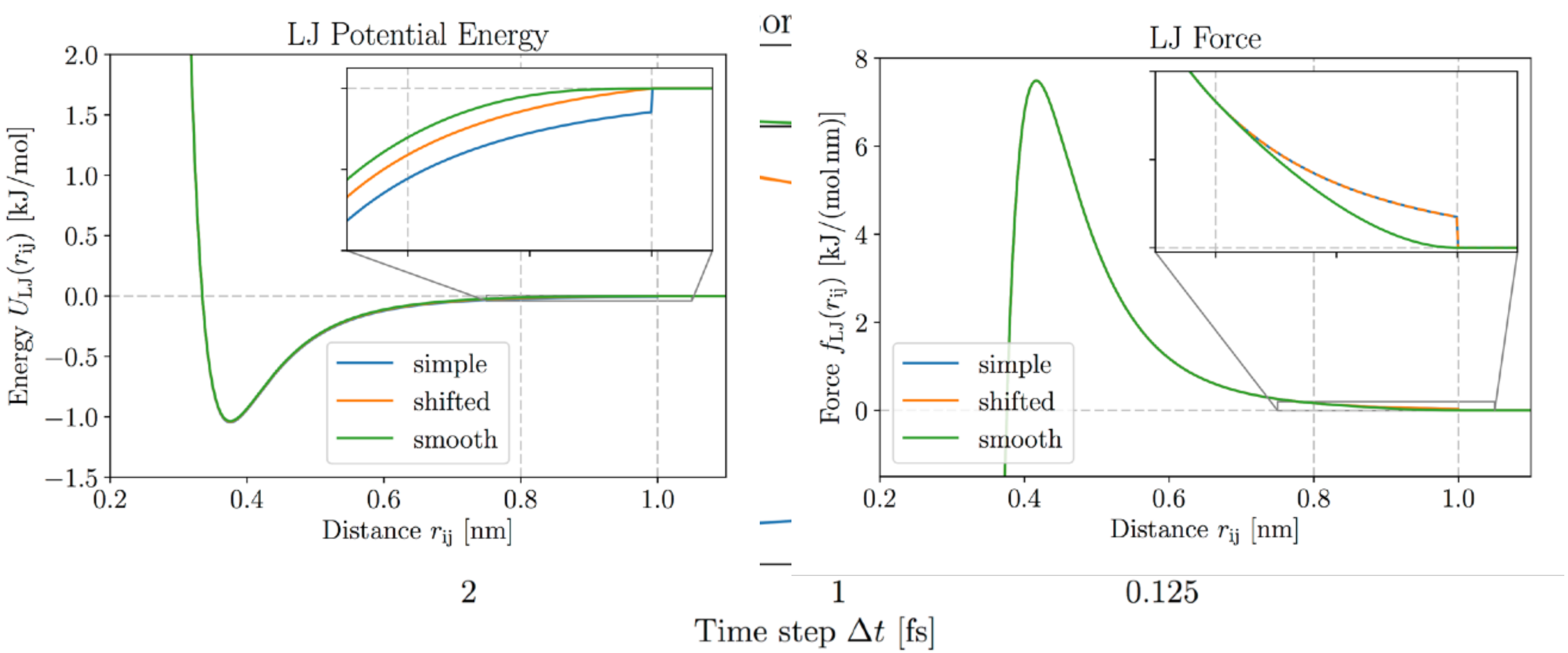
$$\delta E \propto \Delta t^2 \rightarrow \left(\frac{\Delta t_1}{\Delta t_2}\right)^2 = \frac{\delta E_1}{\delta E_2}$$

- non-quadratic behavior indicates lack of symplecticity
  - Integrator algorithm
  - Interaction function
  - Constraint tolerance
- **Powerful bug detection**

Gans & Shalloway, Phys Rev E (2000)

Example: Does my cutoff-scheme violate symplecticity?

- Pure LJ liquid, exact pair list
- Δt = [4,2,1,0.5,0.25,0.125] fs
- 1 nm cutoff: cutoff, shifted, "smooth"



Python module: **`physical-validation`**

Two major parts:

Tests

```
kinetic_energy.py
  distribution()
  equipartition()

ensemble.py
  check()

integrator.py
  convergence()
```

Go to code!

Class representing simulation results, communicates with tests

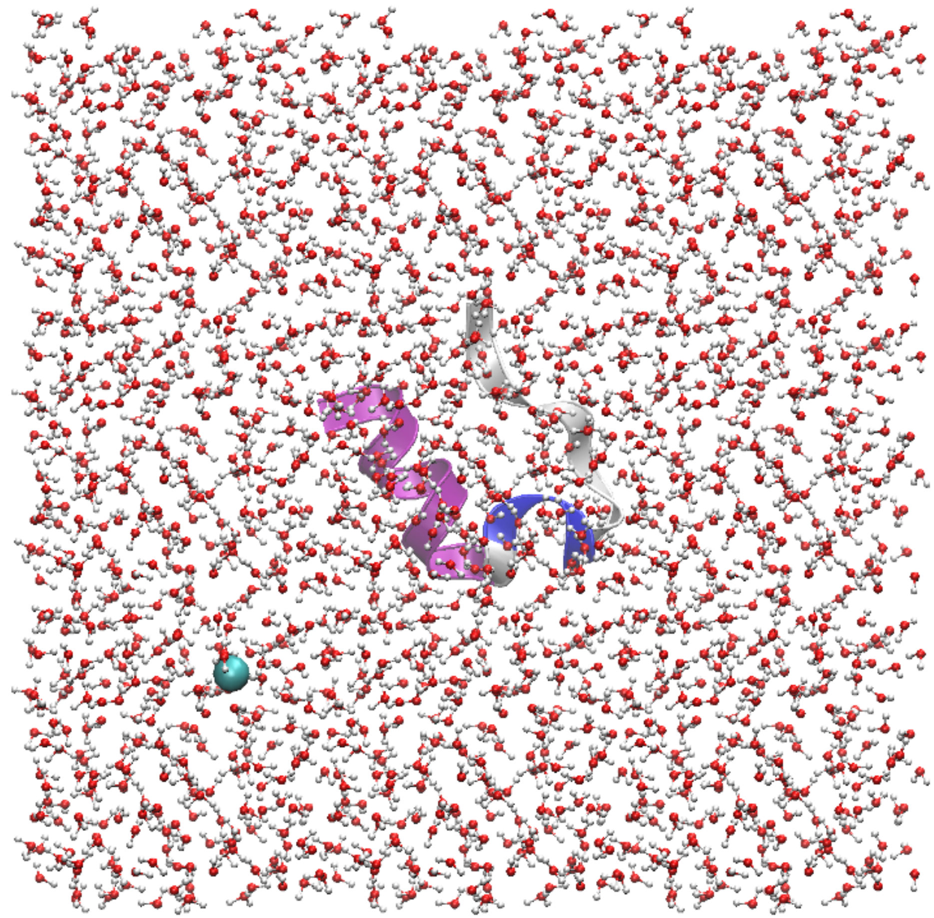
`SimulationData`

Parsers:

- GROMACS
- LAMMPS (beta)
- Flat-file or numpy array
- More to come!

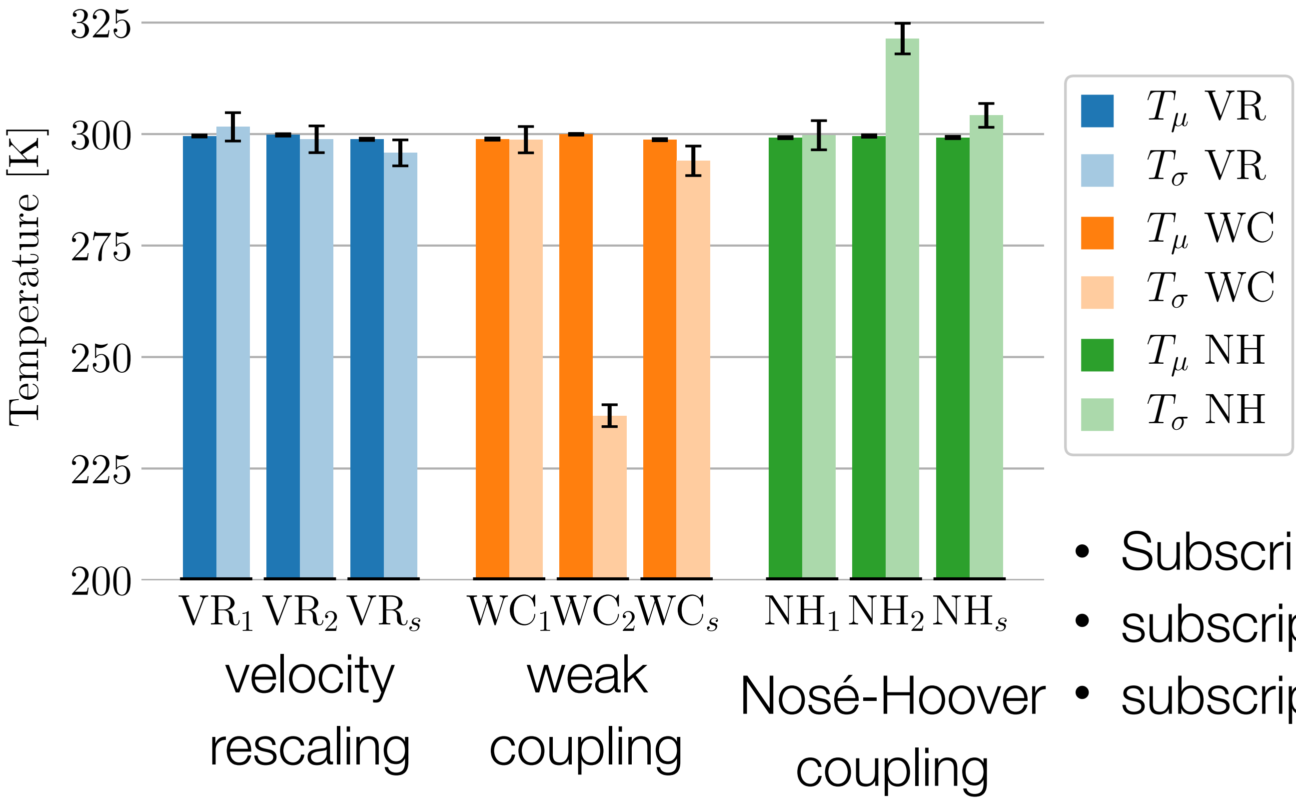
Equipartition: A solvated protein

- Trp-cage miniprotein
- Solvated in water
- Different thermostats, different coupling schemes:
  - system
  - protein, solvent separately
  - solvent alone



How do multiple thermostats on the system affect the KE distribution of the protein?

Effective temperatures of the protein alone



- Subscript 1 = (system)
- subscript 2 = (protein, solvent)
- subscript S = (solvent only)

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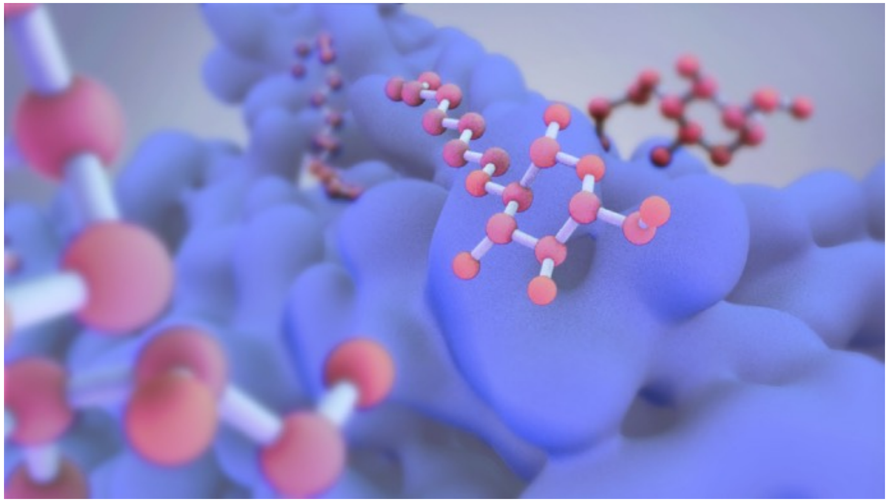
PEBCAK: What about the people?

Problem exists between chair and keyboard

The Living Journal of Computational Molecular Science
http://www.livecomsjournal.org



- A journal for articles that can and *should* be updated
- Article types include best practices for molecular simulation, high quality tutorial, and perpetual reviews
- Will help improve reproducibility and quality of simulations eliminating error
- Please look for the first issue this fall, and consider submitting!

Outlook and Conclusions

- Wide usage of molecular simulation calls for simple-to-use physical validation tools that can be automated.
  - Integration in GROMACS testing to harden code base
- We can validate kinetic energy, ensemble and integrator
- **`physical-validation`** analysis, useable for many codes, at http://physical-validation.readthedocs.io.
- Interested in extensions? → michael.shirts@colorado.edu

Make physical validation a standard MM sanity check for developers and users!