# Regulated Dynamics: a new approach to MTS integration

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# The Middle Integration Scheme

Massive Nosé-Hoover equations:

$$\dot{r}_i = \frac{p_i}{m_i}$$

$$\dot{p}_i = F_i - \frac{p_{\eta_i}}{Q_i} p_i$$

$$\dot{p}_{\eta_i} = \frac{p_i^2}{m_i} - kT$$

Middle-scheme integration step:

$$e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr}} e^{\frac{\Delta t}{2}\mathcal{L}_r^{tr}} \underbrace{e^{\frac{\Delta t}{2}\mathcal{L}_p^{sc}} e^{\Delta t \mathcal{L}_{p\eta}^{tr}} e^{\frac{\Delta t}{2}\mathcal{L}_p^{sc}}}_{e^{\Delta t \mathcal{L}_{\mathrm{bath}}}} e^{\frac{\Delta t}{2}\mathcal{L}_r^{tr}} e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr}}$$

Zhang et al., JCP 147 (2017)
DOI: 10.1063/1.4991621

Zhang et al., JPCA 123 (2019)
DOI: 10.1021/acs.jpca.9b02771

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$$e^{t\mathcal{L}_p^{tr}} \; : \; \begin{cases} \dot{r}_i = 0 \\ \dot{p}_i = F_i \\ \dot{p}_{\eta_i} = 0 \end{cases}$$

solution : $p_i(t) = p_i^0 + F_i^0 t$

$$e^{t\mathcal{L}_p^{sc}} \; : \; \begin{cases} \dot{r}_i = 0 \\ \dot{p}_i = -\frac{p_{\eta_i}}{Q_i} p_i \\ \dot{p}_{\eta_i} = 0 \end{cases}$$

solution : $p_i(t) = p_i^0 e^{-\frac{p_{\eta_i}^0}{Q_i} t}$

# Reference-System Propagator Algorithm

Double time-scale Nosé-Hoover equations:

$$\dot{r}_i = \boxed{\frac{p_i}{m_i}} \qquad \dot{p}_i = \boxed{F_i^s} + \boxed{F_i^f} - \boxed{\frac{p_{\eta_i}}{Q_i} p_i} \qquad \dot{p}_{\eta_i} = \boxed{\frac{p_i^2}{m_i} - kT}$$

Tuckerman et al., JCP 97, 1992
DOI: 10.1063/1.463137

Middle-scheme RESPA integrator:

$$e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr,s}} \left[ e^{\frac{\Delta t}{2n}\mathcal{L}_p^{tr,f}} e^{\frac{\Delta t}{2n}\mathcal{L}_r^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_p^{sc}} e^{\frac{\Delta t}{n}\mathcal{L}_{p\eta}^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_p^{sc}} e^{\frac{\Delta t}{2n}\mathcal{L}_r^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_p^{tr,f}} \right]^n e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr,s}}$$

# Resonance Artifacts

- Outer time step “numerically” resonates with fast modes of motion
- Resonance impairs energy conservation and integration accuracy
- Limits maximum attainable time-step size (~5 fs)

# The Isokinetic Approach

Isokinetic Nosé-Hoover equations:

$$\dot{r}_i = v_i$$

$$\dot{v}_i = \frac{F_i}{m_i} - \lambda_i v_i$$

$$\left.\begin{aligned} \dot{v}_{1,i,j} &= -\lambda_i v_{1,i,2} - v_{2,i,j} v_{1,i,j} \\ \dot{v}_{2,i,j} &= \frac{1}{Q_2}\left(Q_1 v_{1,i,j}^2 - kT\right) \end{aligned}\right\} j = 1, \cdots, L$$

Minary et al., PRL 93 (2004)
DOI: 10.1103/PhysRevLett.93.150201

Isokinetic constraints:

$$\boxed{m_i v_i^2 + \frac{Q_1 L}{L+1} \sum_{j=1}^{L} v_{1,i,j}^2 = LkT}$$

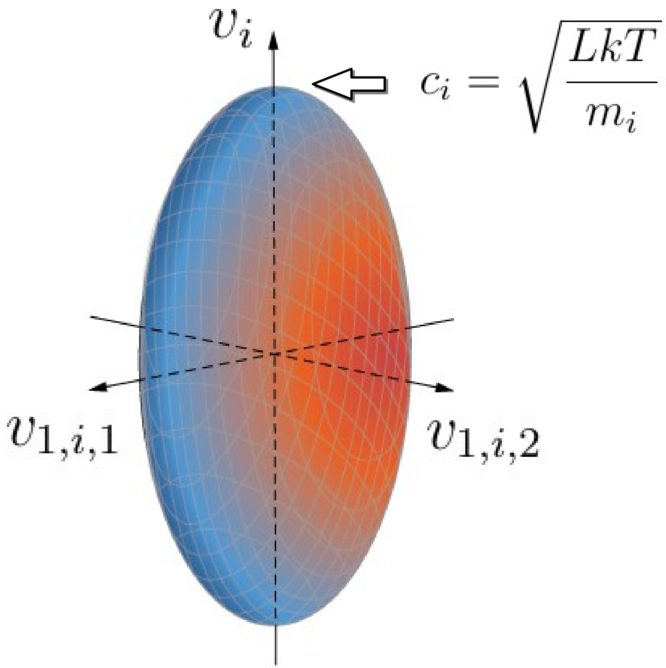
- Changes the dynamics
- Samples coordinates correctly

Leimkuhler et al., Mol. Phys. 111 (2013)
DOI: 10.1080/00268976.2013.844369

# The Isokinetic Approach

Isokinetic constraints:

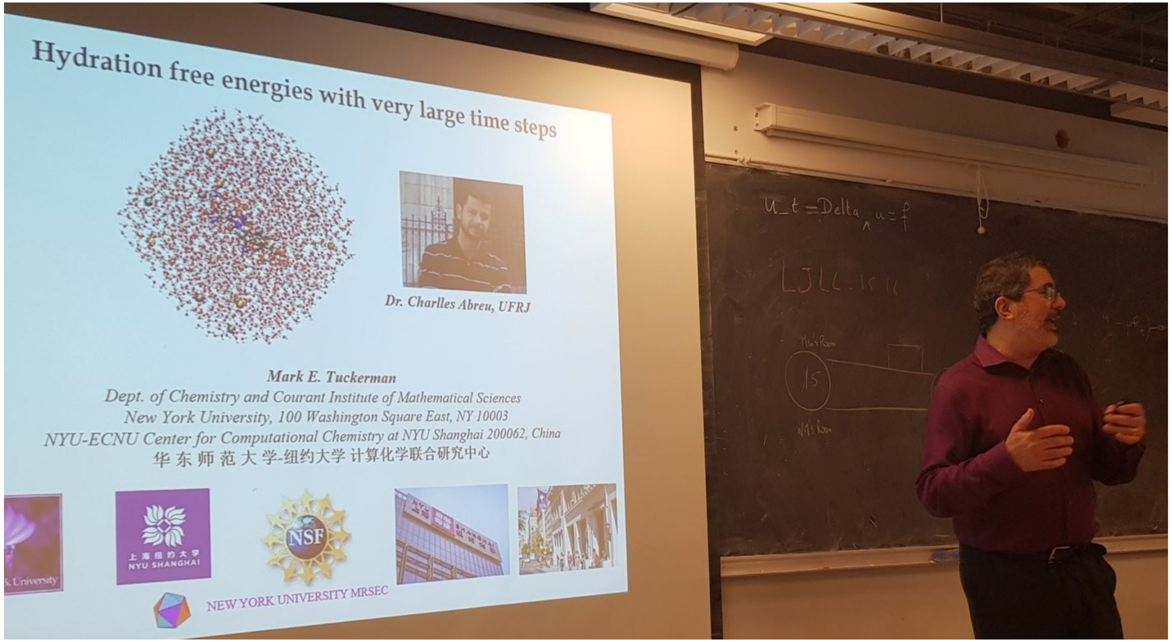
$$\boxed{m_i v_i^2 + \frac{Q_1 L}{L+1} \sum_{j=1}^{L} v_{1,i,j}^2 = LkT}$$

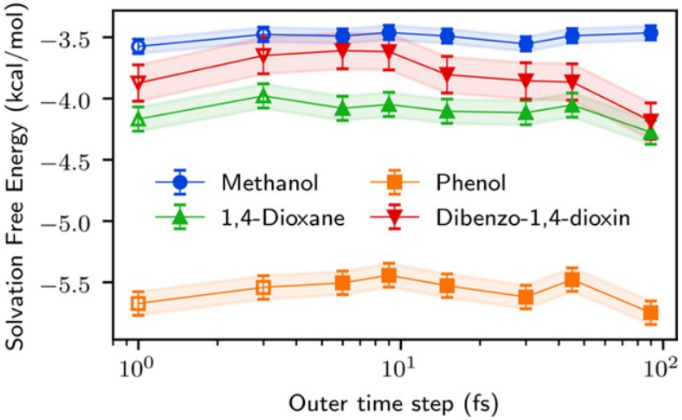


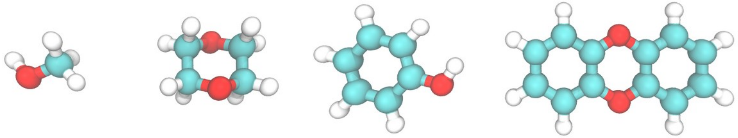
# Stochastic Isokinetic N-H (RESPA): SIN(R)

TINKER Workshop 2019 (Paris)

Abreu and M. Tuckerman, JCTC (2020)
DOI: 10.1021/acs.jctc.0c00698



# Isokinetic Nosé-Hoover (RESPA)

Double time-scale Isokinetic N-H equations:

$$\dot{r}_i = v_i$$

$$\dot{v}_i = \frac{F_i^s}{m_i}\left(1 - \frac{m_i v_i^2}{LkT}\right) + \frac{F_i^f}{m_i}\left(1 - \frac{m_i v_i^2}{LkT}\right) + \left[\frac{Q_1}{(L+1)kT}\sum_{j=1}^{L} v_{2,i,j} v_{1,i,j}^2\right] v_i$$

$$\dot{v}_{1,i,j} = \left(-\frac{F_i^s v_i}{LkT} v_{1,i,j}\right) + \left(-\frac{F_i^f v_i}{LkT} v_{1,i,j}\right) + \left[\frac{Q_1}{(L+1)kT}\sum_{k=1}^{L} v_{2,i,k} v_{1,i,k}^2 - v_{2,i,j}\right] v_{1,i,j}$$

$$\dot{v}_{2,i,j} = \frac{Q_1 v_{1,i,j}^2 - kT}{Q_2}$$

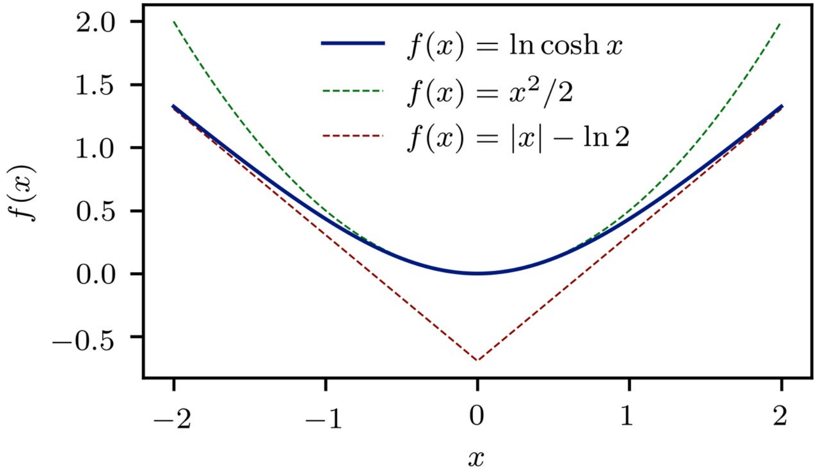
Middle-RESPA integrator:

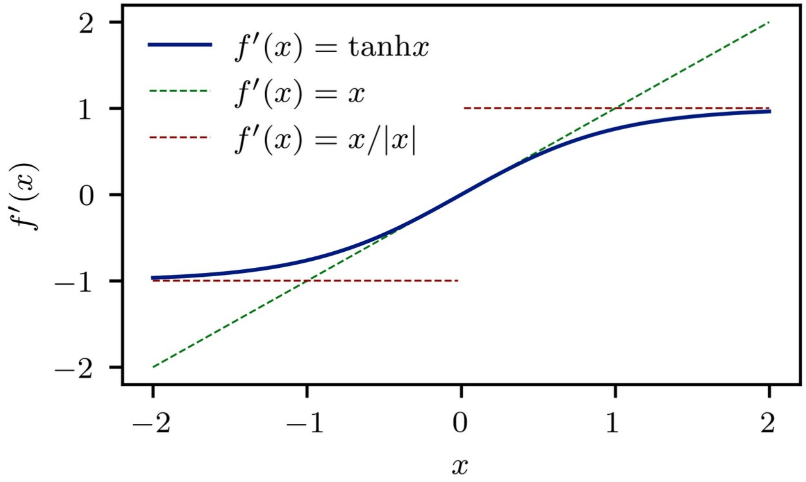
$$e^{\Delta t \mathcal{L}} = e^{\frac{\Delta t}{2}\mathcal{L}_{\mathrm{B}}^{s}} \left[ e^{\frac{\Delta t}{2n}\mathcal{L}_{\mathrm{B}}^{f}} e^{\frac{\Delta t}{2n}\mathcal{L}_{r}^{tr}} \underbrace{e^{\frac{\Delta t}{2n}\mathcal{L}_{\mathrm{IsoK}}} e^{\frac{\Delta t}{n}\mathcal{L}_{p\eta}^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_{\mathrm{IsoK}}}}_{e^{\frac{\Delta t}{n}\mathcal{L}_{\mathrm{bath}}}} e^{\frac{\Delta t}{2n}\mathcal{L}_{r}^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_{\mathrm{B}}^{f}} \right]^{n} e^{\frac{\Delta t}{2}\mathcal{L}_{\mathrm{B}}^{s}}$$

# The Regulated Dynamics Approach

$$\mathcal{H} = \sum_{i=1}^{3N} \frac{p_i^2}{2m_i} + U(\mathbf{r})$$

$$v_i = \frac{\partial \mathcal{H}}{\partial p_i} = \frac{p_i}{m_i}$$



# The Regulated Dynamics Approach

$$\mathcal{H} = \sum_{i=1}^{3N} \frac{p_i^2}{2m_i} + U(\mathbf{r}) \qquad \rightarrow \qquad \mathcal{H} = \sum_{i=1}^{3N} m_i c_i^2 \ln\cosh\left(\frac{p_i}{m_i c_i}\right) + U(\mathbf{r})$$

$$v_i = \frac{\partial \mathcal{H}}{\partial p_i} = \frac{p_i}{m_i} \qquad \rightarrow \qquad v_i = \frac{\partial \mathcal{H}}{\partial p_i} = c_i \tanh\left(\frac{p_i}{m_i c_i}\right)$$

From the isokinetic method: $c_i = \sqrt{\frac{LkT}{m_i}}$

Generalized Equipartition: $\langle p_i v_i \rangle = kT$

# The Regulated Dynamics Approach

Double time-scale Regulated N-H equations:

$$\dot{r}_i = v_i$$

$$\dot{p}_i = F_i^s + F_i^f - \frac{p_{\eta_i}}{Q_i} p_i$$

$$\dot{p}_{\eta_i} = p_i v_i - kT$$

$$\cancel{v_i = \frac{p_i}{m_i}}$$

$$v_i = c_i \tanh\left(\frac{p_i}{m_i c_i}\right)$$

Middle-scheme RESPA integrator:

$$e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr,s}} \left[ e^{\frac{\Delta t}{2n}\mathcal{L}_p^{tr,f}} e^{\frac{\Delta t}{2n}\mathcal{L}_r^{tr}} \underbrace{e^{\frac{\Delta t}{2n}\mathcal{L}_p^{sc}} e^{\frac{\Delta t}{n}\mathcal{L}_{p\eta}^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_p^{sc}}}_{e^{\frac{\Delta t}{n}\mathcal{L}_{\mathrm{bath}}}} e^{\frac{\Delta t}{2n}\mathcal{L}_r^{tr}} e^{\frac{\Delta t}{2n}\mathcal{L}_p^{tr,f}} \right]^n e^{\frac{\Delta t}{2}\mathcal{L}_p^{tr,s}}$$

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https://doi.org/10.1080/00268976.2021.1923848

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## Hamiltonian based resonance-free approach for enabling very large time steps in multiple time-scale molecular dynamics

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Chemistry, New York University, New York, NY, USA; [c]Courant Institute of Mathematica
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Topical Review - Computational Methods

## Multiple timescale molecular dynamics with very large time steps: avoidance of resonances

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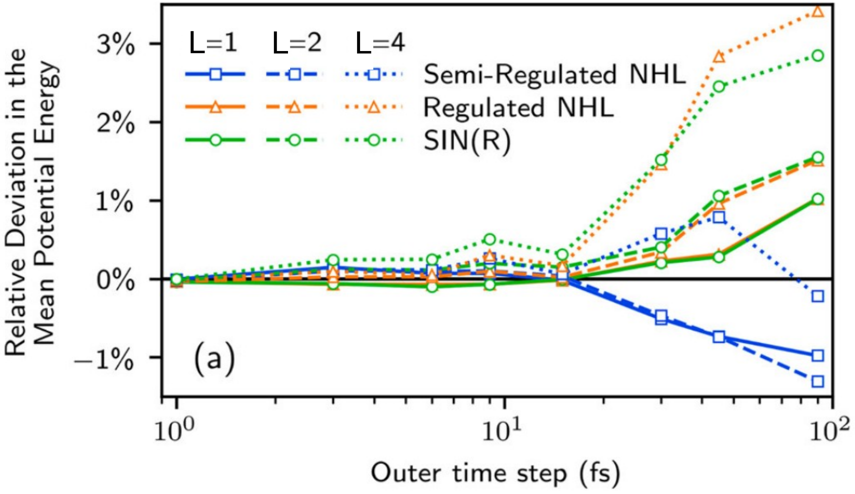
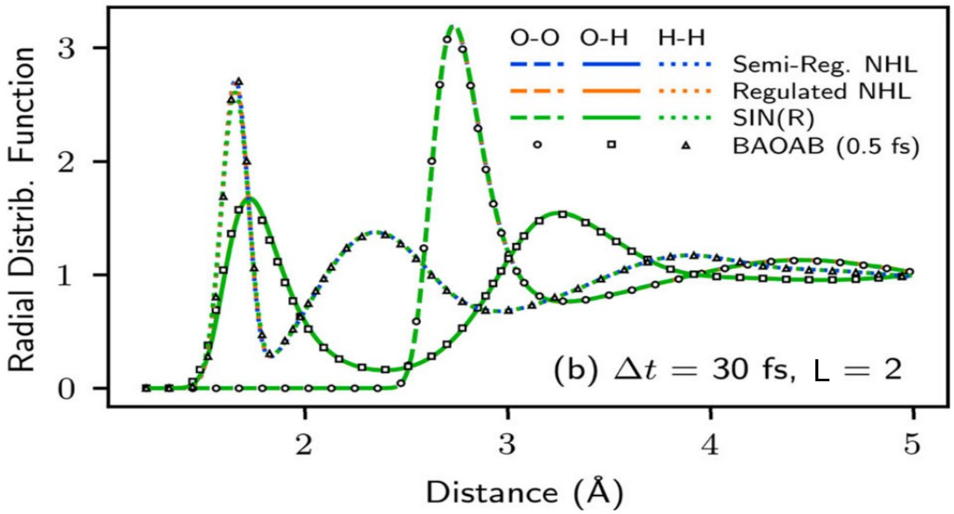
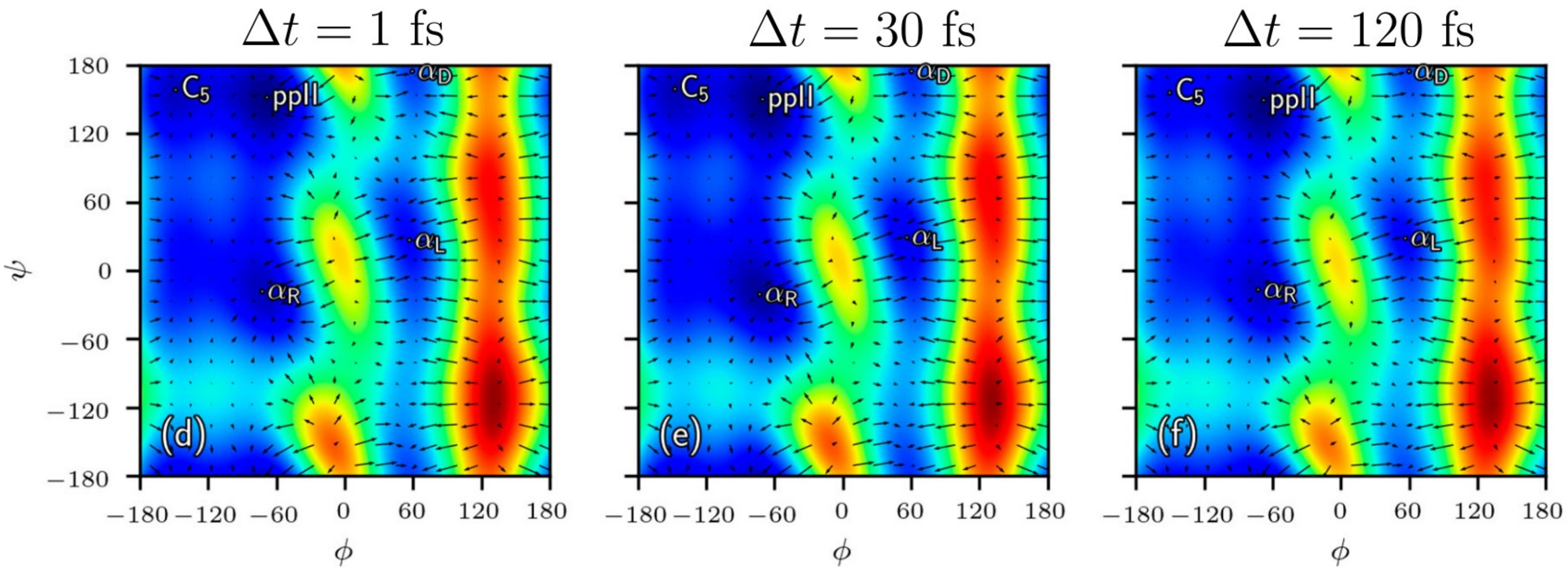
4 NYU-ECNU Center for Computational Chemistry at NYU Shanghai, Shanghai 200062, China

# Liquid SPC-Fw Water - NVT Ensemble - OpenMM

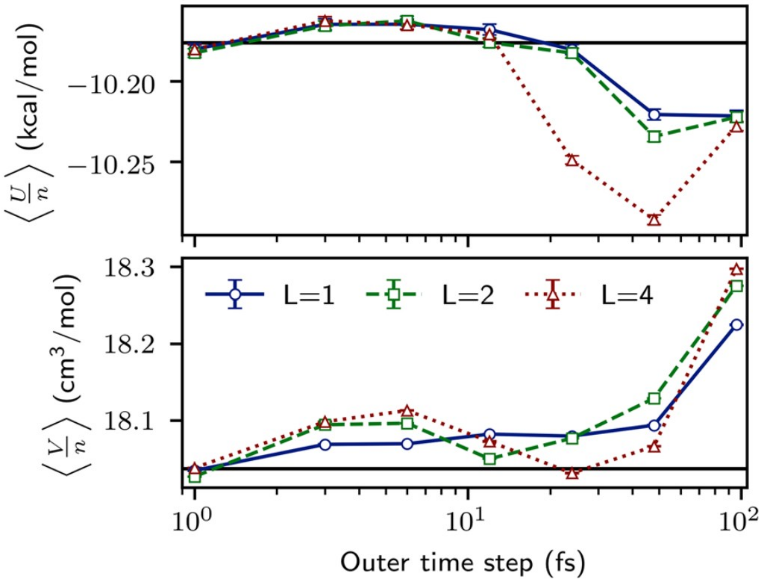


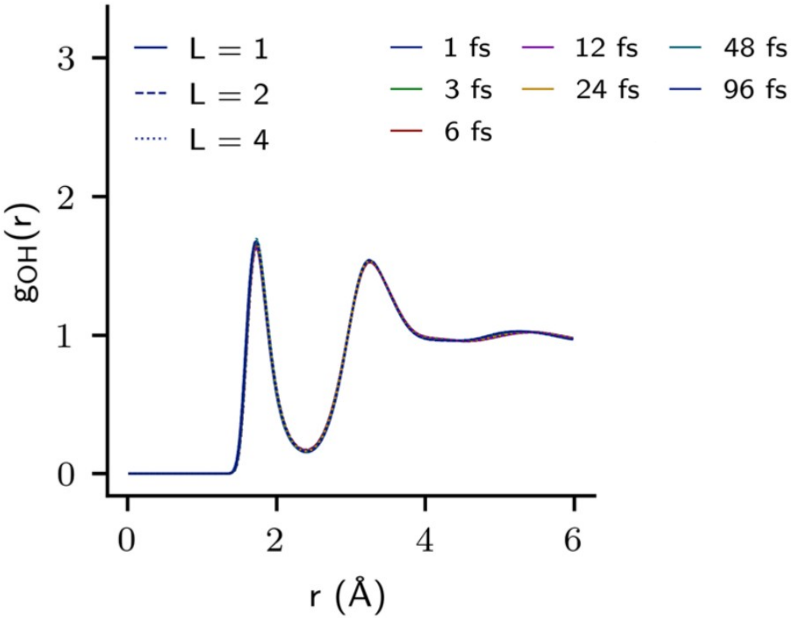



# Alanine Dipeptide in Solution: Enhanced Sampling



# Liquid SPC-Fw Water - NPT Ensemble - LAMMPS



# Conclusion

- Familiar Hamiltonian approach
- Does not require extra variables
- Makes it easy to adapt existing codes
- Extensible to different ensembles

# OpenMM extension available on Github

https://github.com/craabreu/ufedmm

README.md

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## Unified Free Energy Dynamics with OpenMM

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UFEDMM extends OpenMM's Python API so that the user can easily run efficient simulations in extended phase spaces, perform enhanced sampling of systems with barriers and rare events, and compute accurate free-energy surfaces for collective variables or reaction coordinates.