Enhanced Sampling & Metadynamics

Shiv Upadhyay

University of Pittsburgh

October 9, 2018

Molecular Dynamics reminder

Start molecules in some positions (x)

Molecular Dynamics reminder

Start molecules in some positions (x)

Calculate the forces on the molecules based on the derivate of the "forcefield" or potential function

$$F = -\boldsymbol{\nabla}U(x)$$

Molecular Dynamics reminder

Start molecules in some positions (x)

Calculate the forces on the molecules based on the derivate of the "forcefield" or potential function

$$F = -\boldsymbol{\nabla}U(x)$$

Use Newton's second law to get new positions

$$F = ma = m\frac{\partial^2 x}{\partial t^2}$$

Molecular Dynamics reminder

Start molecules in some positions (x)

Calculate the forces on the molecules based on the derivate of the "forcefield" or potential function
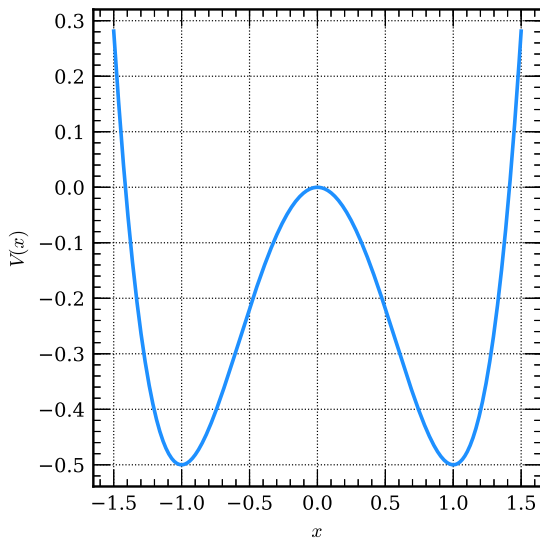
$$F = -\boldsymbol{\nabla}U(x)$$

Use Newton's second law to get new positions
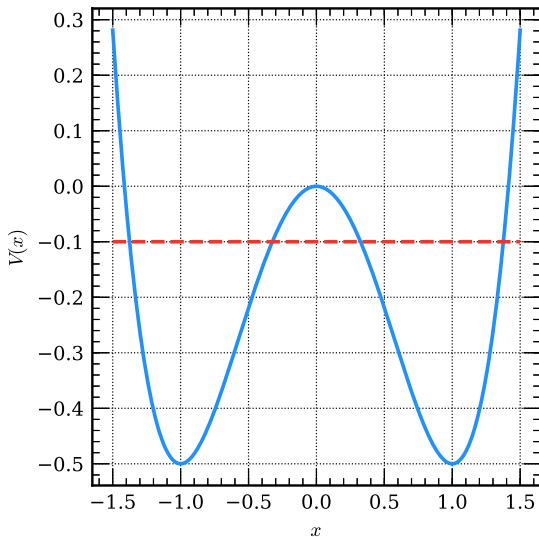
$$F = ma = m\frac{\partial^2 x}{\partial t^2}$$

$$v(t + \Delta t) = v(t) + \frac{1}{2}(a(t) + a(t + \Delta t))\Delta t$$

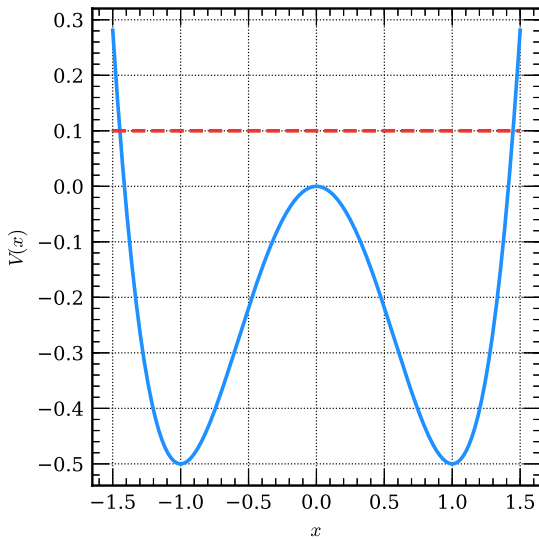$$x(t + \Delta t) = x(t) + v(t)\Delta t + \frac{1}{2}a(t)\Delta t^2$$

Potential Energy Surface

Impossible events

Rare events

# Enhanced sampling... Why do we need it?

Rare events are... rare.

Enhanced sampling... Why do we need it?

Rare events are... rare.

A lot of interesting chemistry is rare. Protein folding, ligand binding, aggregation, etc...

Enhanced sampling... Why do we need it?

Rare events are... rare.

A lot of interesting chemistry is rare. Protein folding, ligand binding, aggregation, etc...

Enhanced sampling lets us simulate more of the interesting chemistry in the same amount of simulation time.

Enhanced sampling... How do we do it?
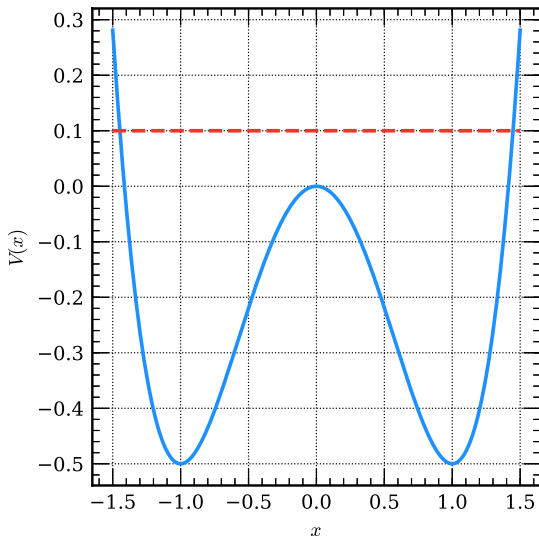
# Enhanced sampling... How do we do it?

We can control T and the PES.[1]

- **Temperature** - "Tempering" methods control the temperature to overcome barriers
- **PES**:
    - Bias the PES by adding another potential to limit sampling of the same area
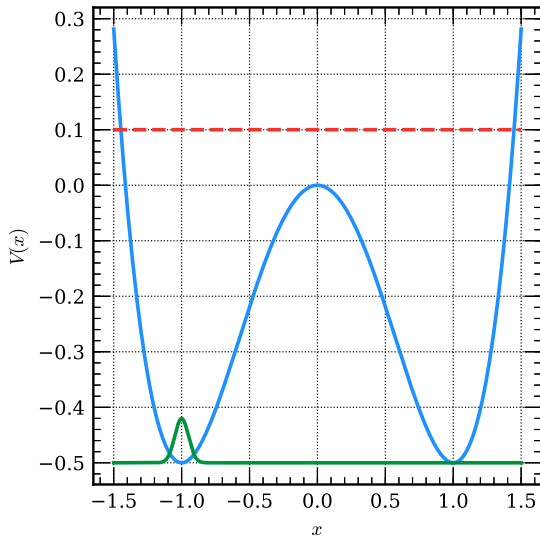   - Modify the forcefield to raise minima

---

[1] Abrams, C.; Bussi, G. *Entropy* **2014**, *16*, 163–199, Miao, Y.; McCammon, J. A. *Molecular Simulation* **2016**, *42*, 1046–1055.
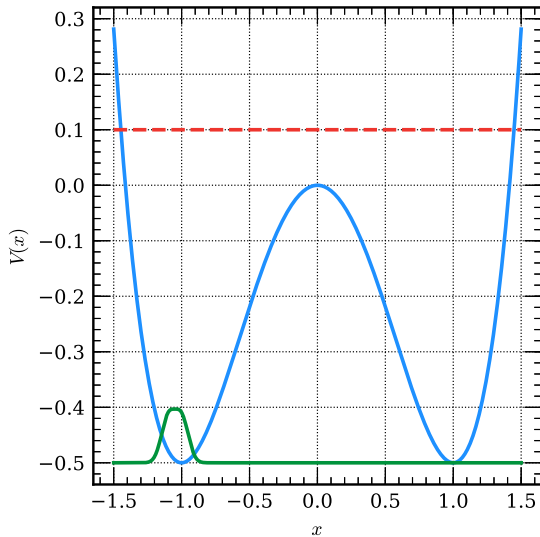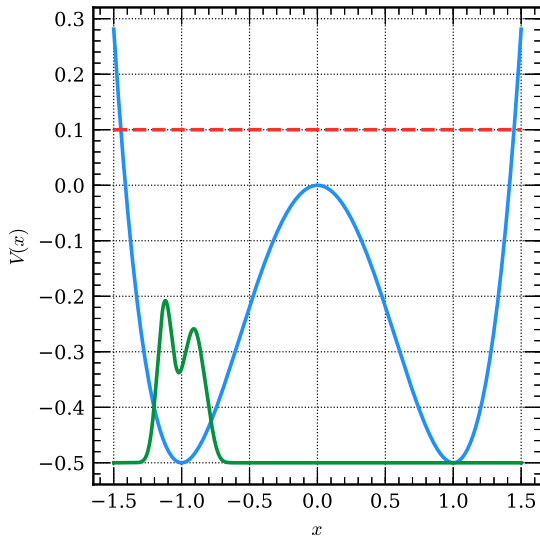
Replica Exchange/Parallel Tempering
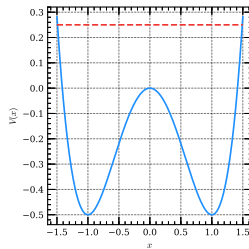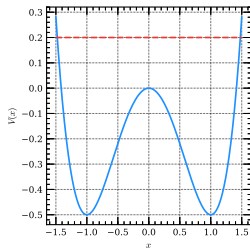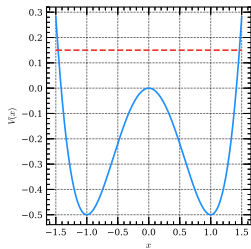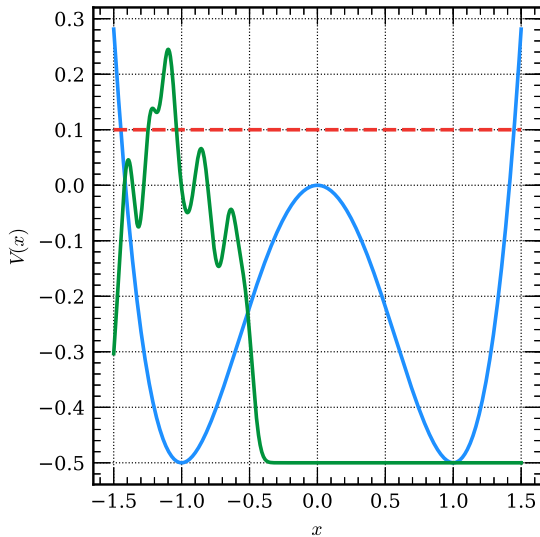
Metadynamics

Metadynamics

Metadynamics

Metadynamics

Accelerated Molecular Dynamics