Neural SHAKE:
Geometric Constraints in Graph Generative Models

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Molecule Conformations

- same molecule takes different 3d structures

  => different conformations

- Important for
  - understanding chemical reactions
  - protein-ligand interactions => drug design
  - understanding cause of diseases (e.g. Alzheimer)
  - material design

- Probability distribution of 3d conformations: “Boltzmann distribution”

Boltzmann distribution

- “Boltzmann distribution” :

$$p(x) = \frac{1}{Z} e^{-\frac{1}{kT} E(x)}$$

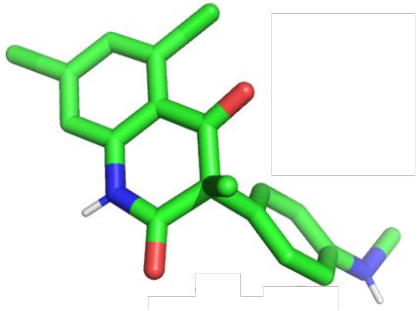
Energy E(x) of conformation x

normalization constant Z

constant k

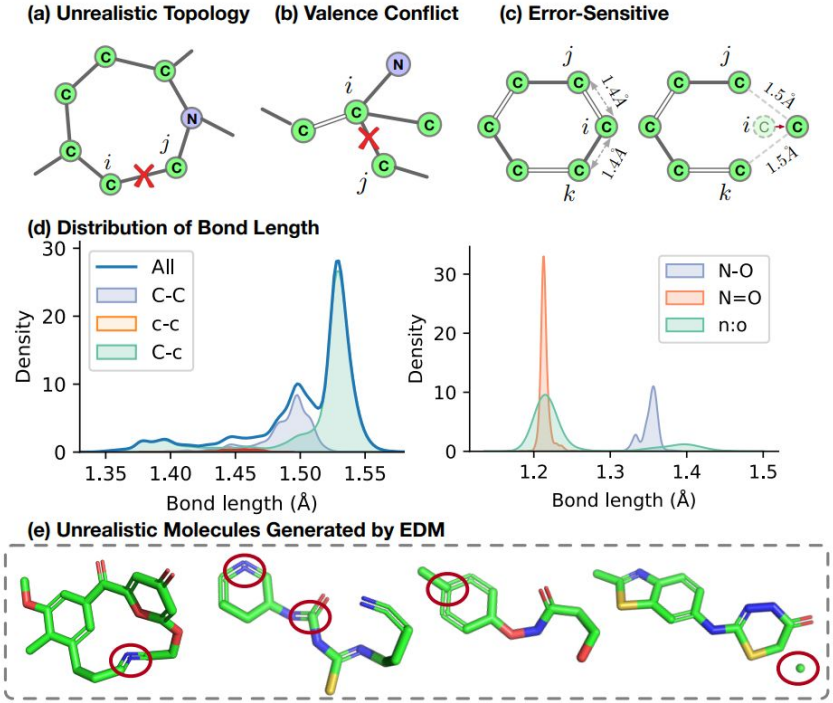
temperature T

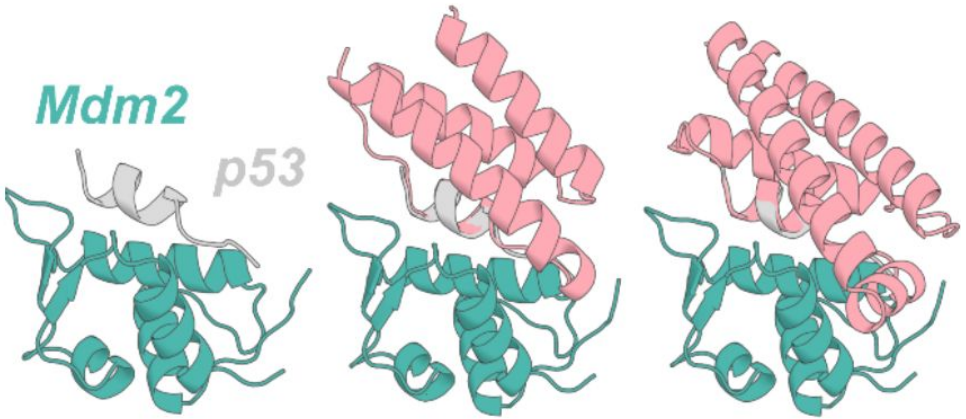
- Problem setup:
  - E(x): can be estimated
  - Z: difficult to estimate for large systems



- Goals:
  - Sample from p(x) more efficiently
  - Sample subspaces of p(x) defined by geometrical constraints

Why Constraints in Molecular Generative Models

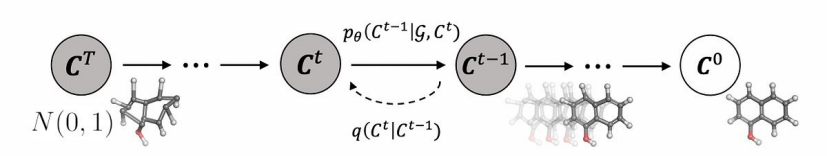


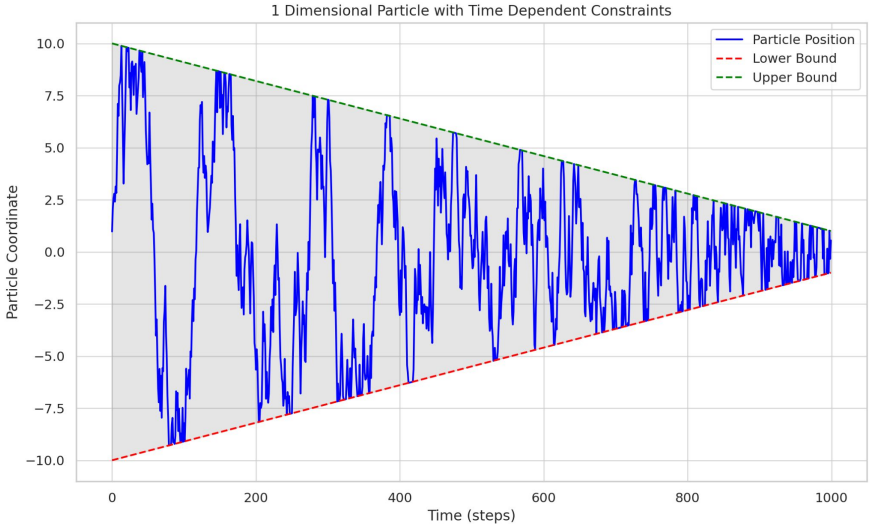


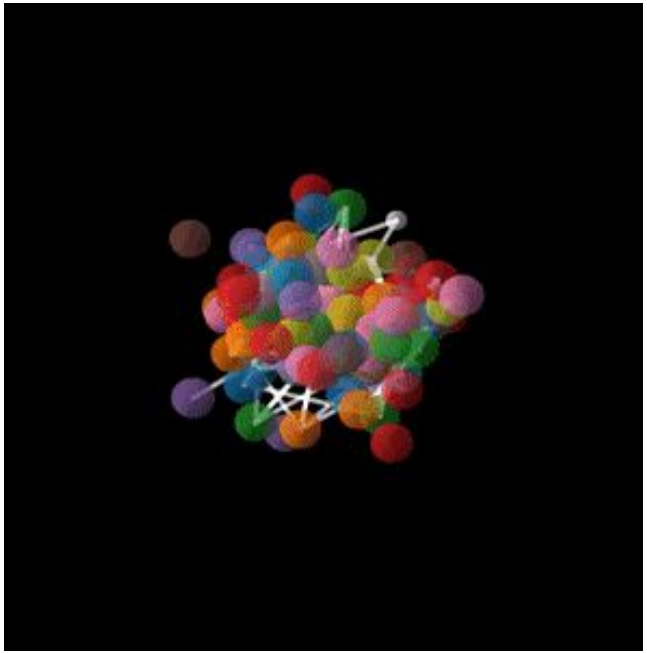
Taken from De novo design of protein structure and function with RFdiffusion, Baker et. al

Sampling molecule conformation:

- Start from noise, transform to target distribution



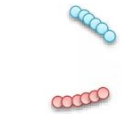




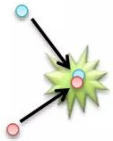
Gif from Equivariant Diffusion for Molecule Generation in 3D Welling et. al

Shake Algorithm in MD vs Diffusion

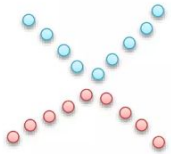
speed



Too short - computation needlessly slow



Too long - errors result from approximations



Just right - errors acceptable, maximum speed

Sampling subspaces

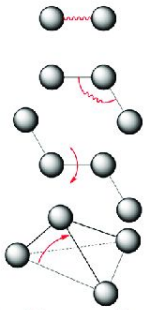
Constrained Diffusion

$$M\frac{d^2X}{dt^2} = -\nabla U - \sum_a \lambda_a \nabla \sigma_a$$

Molecular Dynamics

- Local

$$U(R) = \sum_{bonds} k_r (r - r_{eq})^2 \quad \text{bond}$$
$$+ \sum_{angles} k_\theta (\theta - \theta_{eq})^2 \quad \text{angle}$$
$$+ \sum_{dihedrals} k_\phi (1 + \cos[n\phi - \gamma]) \quad \text{dihedral}$$
$$+ \sum_{impropers} k_\omega (\omega - \omega_{eq})^2 \quad \text{improper}$$
$$+ \sum_{i<j}^{atoms} \varepsilon_{ij} \left[\left(\frac{r_m}{r_{ij}} \right)^{12} - 2 \left(\frac{r_m}{r_{ij}} \right)^{6} \right] \quad \text{van der Waals}$$
$$+ \sum_{i<j}^{atoms} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \quad \text{electrostatic}$$



Generative Dynamics

- Global
  - 1,.., k shot samples
- Parameterized
- Steerable
  - Temperature
  - Conditional
  - …
  - Now, constraint based

Types of Geometric Constraints

What we mainly focus on

Distance Constraint

$$\Delta d_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2} - d_{ij}^{constraint} =$$

Torsion Angle Constraint

$$\cos(\tau_{ijkl}) = \frac{\mathbf{r}_{ij} \times \mathbf{r}_{jk} \cdot \mathbf{r}_{jk} \times \mathbf{r}_{kl}}{|\mathbf{r}_{ij} \times \mathbf{r}_{jk}| \times |\mathbf{r}_{jk} \times \mathbf{r}_{kl}|} - \tau_{ijkl}^{constraint} = 0$$

Bond Angle Constraint

$$\cos(\theta_{ijk}) = \frac{\mathbf{r}_{ij} \cdot \mathbf{r}_{jk}}{|\mathbf{r}_{ij}| \times |\mathbf{r}_{jk}|} - \theta_{ijk}^{constraint} = 0$$

Molecular Property generation

Dipole Moment Calculation

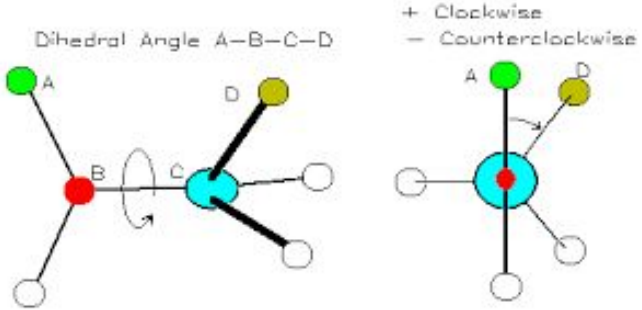
$$\vec{\mu} = \sum_{i=1}^{N} q_i \vec{r}_i$$

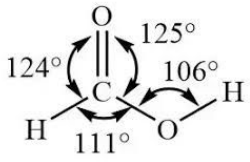
Magnitude of the Dipole Moment

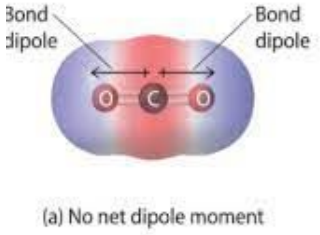
$$|\vec{\mu}| = \sqrt{\mu_x^2 + \mu_y^2 + \mu_z^2}$$

Polarization Constraint

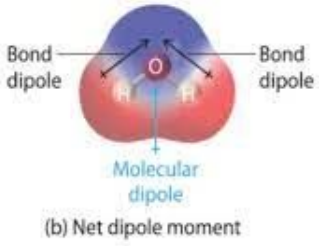
$$|\vec{\mu}| - \mu^{constraint} = 0$$







(a) No net dipole moment



(b) Net dipole moment

Neural SHAKE

Set of distance constraints

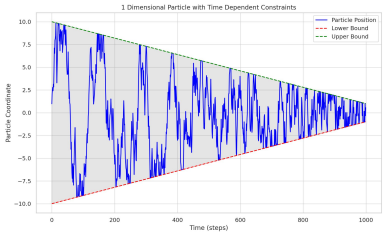
Reverse Diffusion Process

$$dx = \sqrt{2D}\left(I - \frac{\nabla\sigma_{d_{ij}}(t)\nabla\sigma_{d_{ij}}(t)^T}{\|\nabla\sigma_{d_{ij}}(t)\|^2}\right)dB - D\nabla\log p_t(x)dt$$

We do not consider the forward process here because we do not train our model

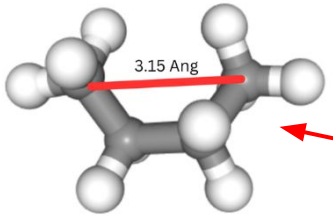
Constraint Scheduler

$$s(t) = \frac{1}{1 + e^{-\beta(t-t_0)}}$$

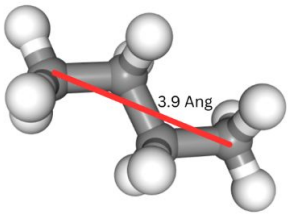


Butane Energy Profile

Distances

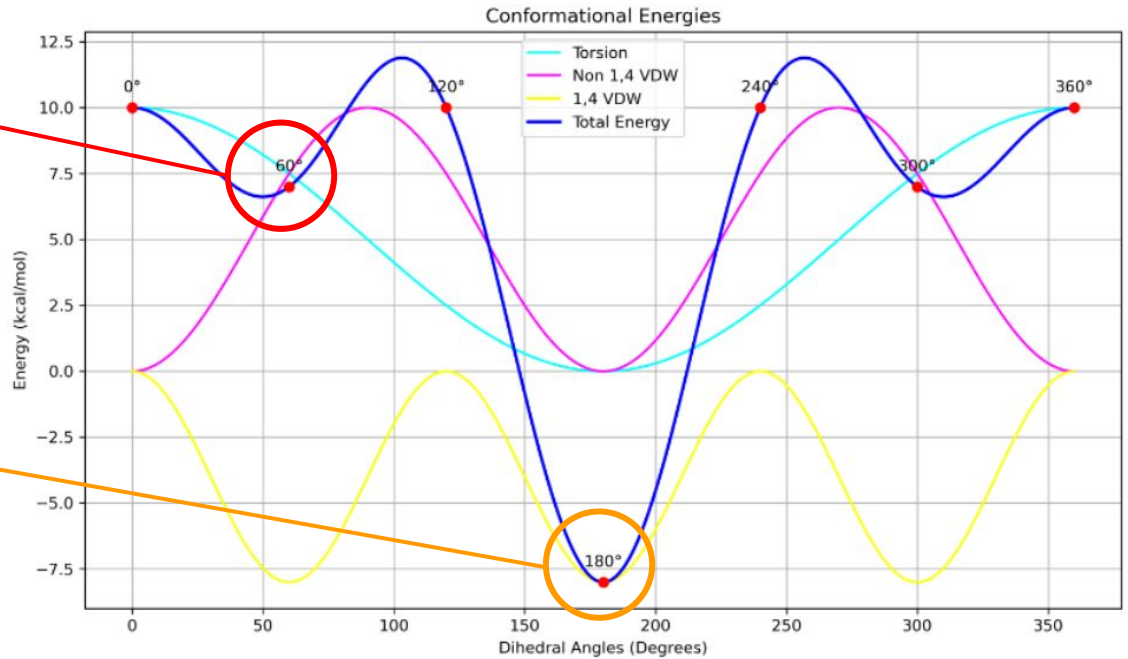


(a) 3.15 Å distance constraint.



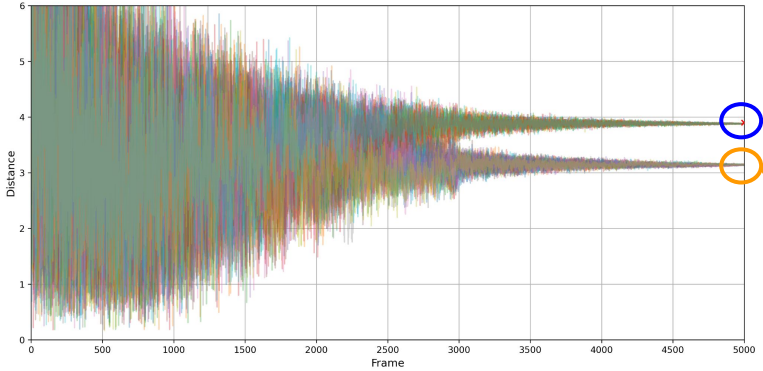
(b) 3.9 Å distance constraint.

Torsions

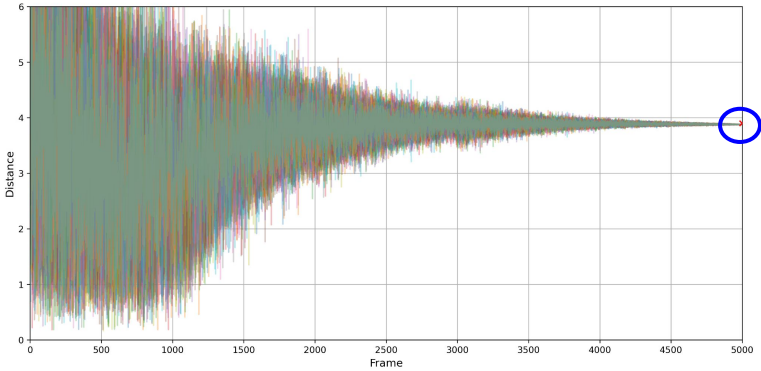


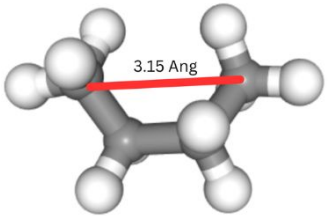
Using Diffusion to Sample Subspaces of Molecular Conformations

Unconstrained



Constrained





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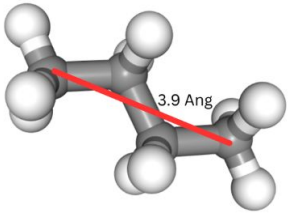
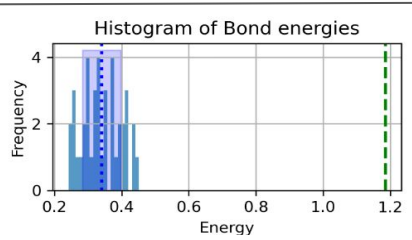
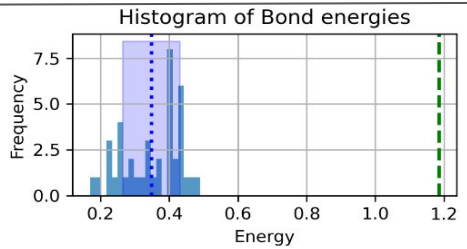
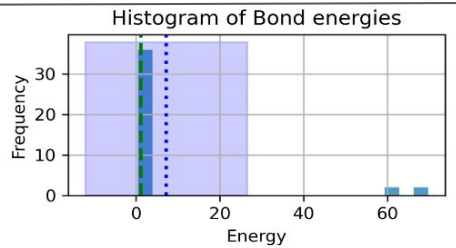
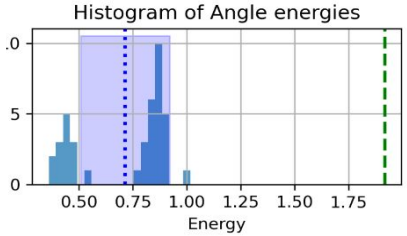
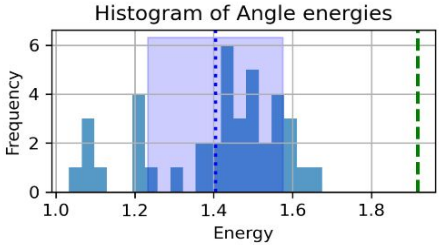
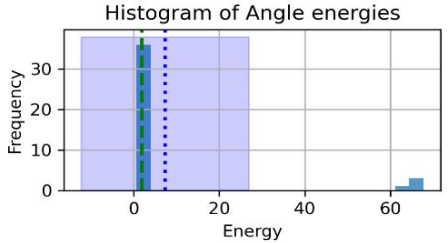
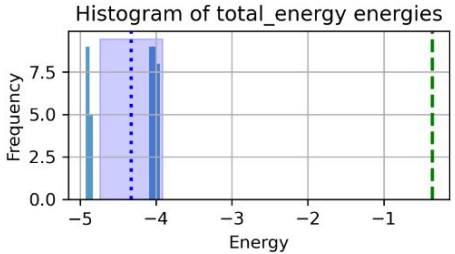
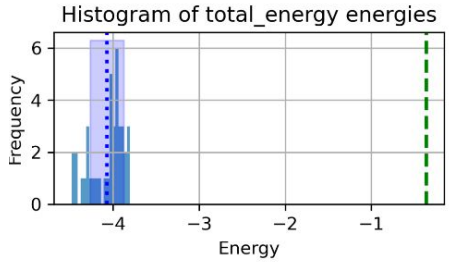
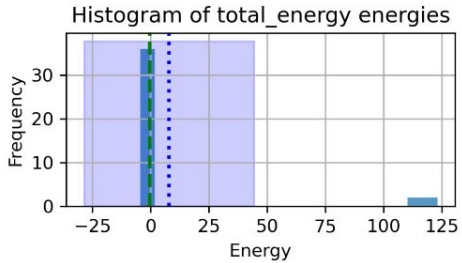


(b) 3.9 Å distance constraint.

Butane Energy Analysis: Bonds & Angles & Total

	Unconditional	Neural SHAKE	Guidance
Bonds			
Angles			
Total			

Butane Energy Analysis: Torsion and Van der Waals

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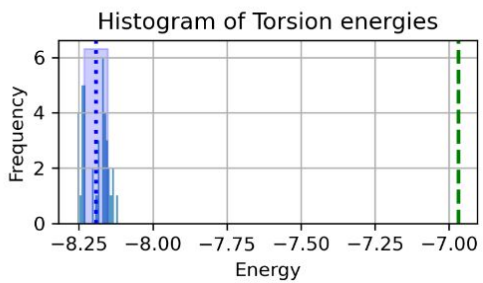
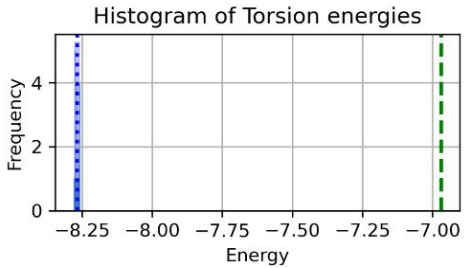
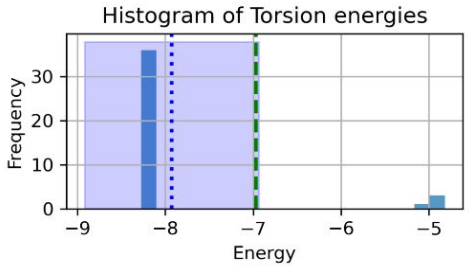
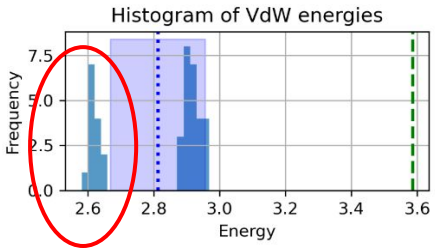
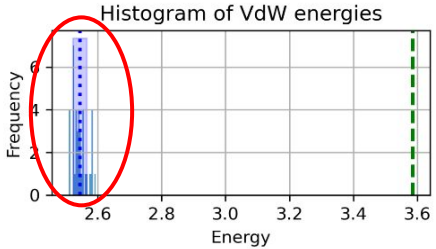
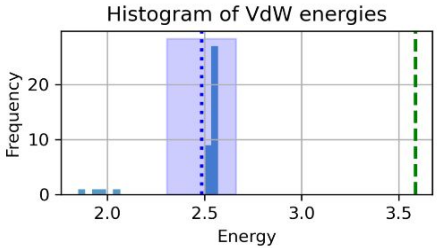
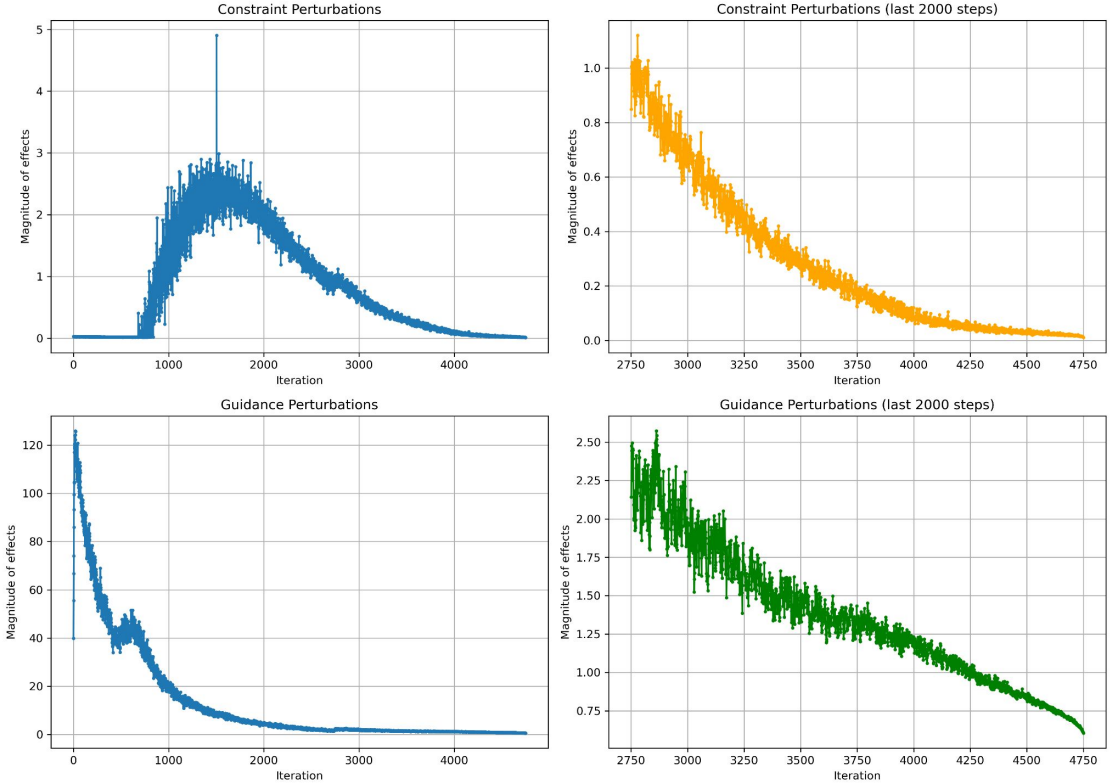
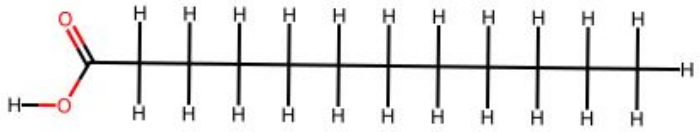
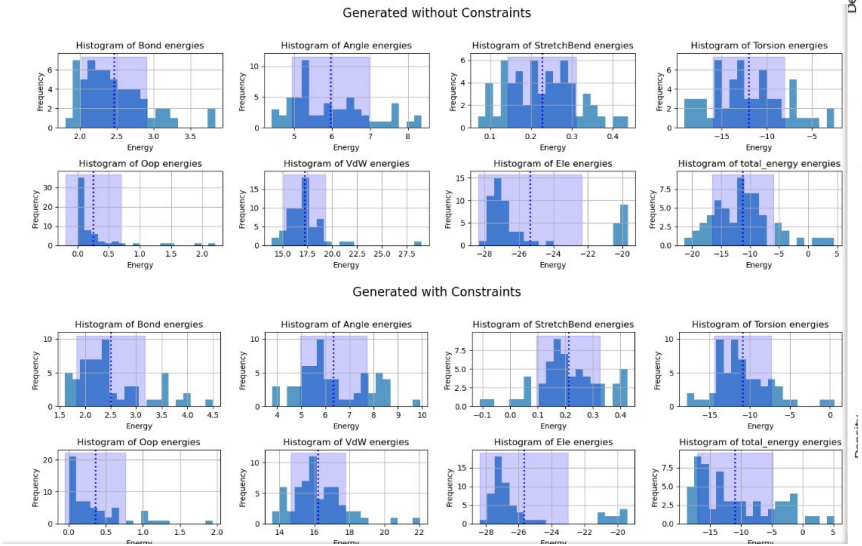
Torsion			
VdWs			

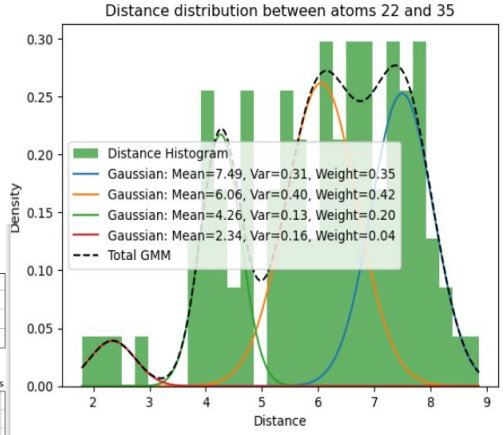
Neural SHAKE vs Guidance

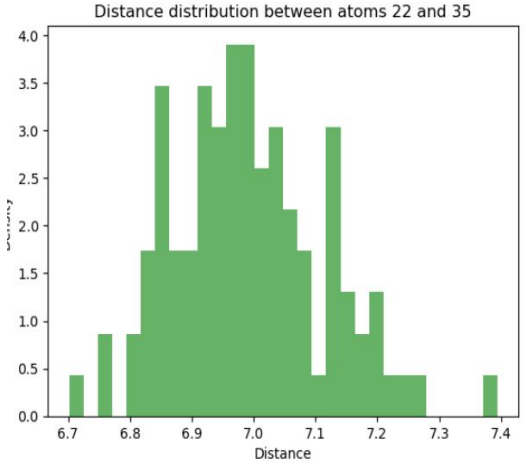


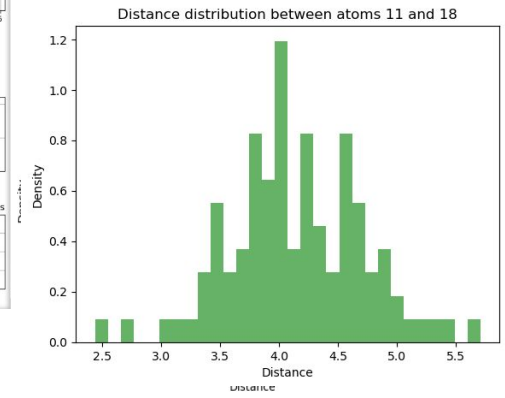
Constraining **Distributions**

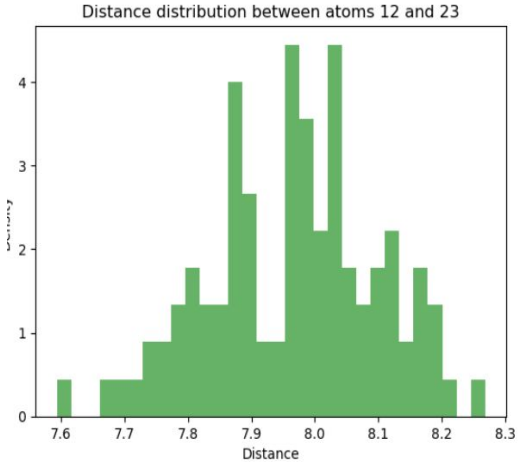






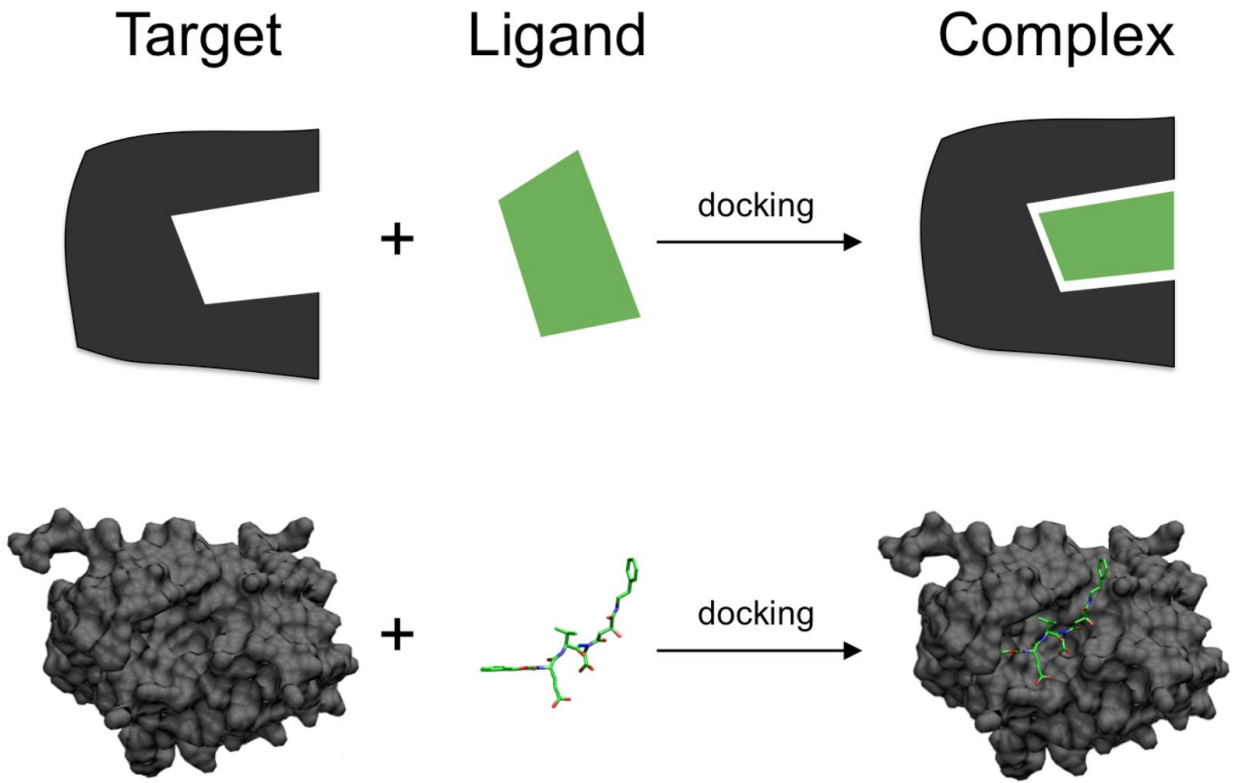






Constraint Based Generative Docking

- Take pretained confomer / molecular generative model
- Define auxiliary points of the binding pocket to constrain the conformer to
- Add additional constraints for local protein - ligand interactions



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Thank you

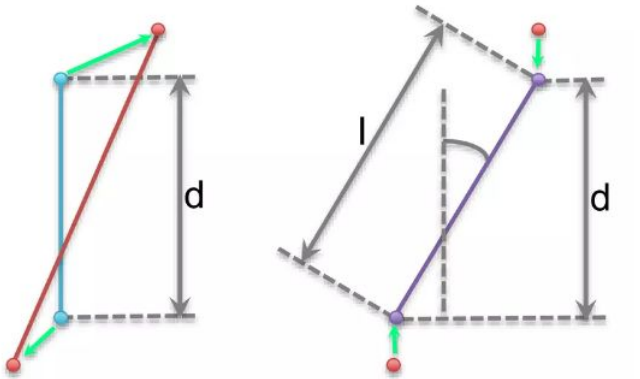
for your attention.

Shake Algorithm Cont.

1. **Initialization**: Start with initial positions x_i and an initial guess for the Lagrange multipliers λ.
2. **Iteration**: Repeat until convergence:
   - Update positions using $x_i^{(n)} = x_i^{(n-1)} - \sum_b \lambda_b^{(n-1)} \nabla \sigma_b(x_i)$.
   - Compute the matrix $A_{\alpha\beta}$ using $A_{\alpha\beta}^{(n-1)} = \nabla \sigma_\alpha(x_i^{(n-1)}) \cdot \nabla \sigma_\beta(x_i)$.
   - Solve the system of equations $\sum_\beta \lambda_\beta^{(n-1)} A_{\alpha\beta}^{(n-1)} = \sigma_\alpha(x_i^{(n-1)})$ to find the new Lagrange multipliers.
   - Check if the constraints $\sigma_\alpha(x_i^{(n)})$ are satisfied within a tolerance; if not, repeat the iteration.

Shake Alg. Cont.

SHAKE algorithm fixes X-H bonds and allows increase of timesteps from 1fs to 2fs.



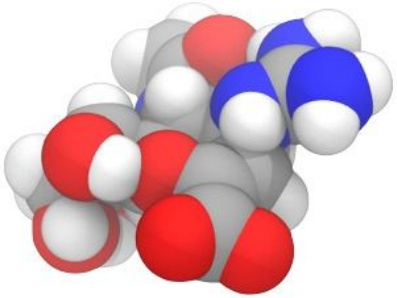
Unconstrained update → Project out forces along the bond -

Molecular Dynamics

t

$x(t)$

$v(t)$



1. Assign velocities to all atoms
2. Calculate forces on all atoms
3. Use Newton's second law to calculate acceleration on each atom

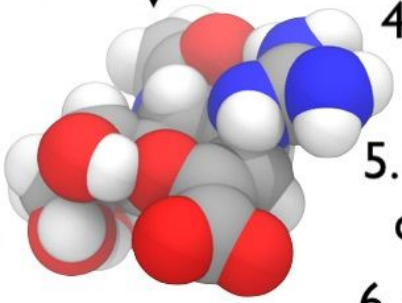
$$F = ma$$

4. Calculate velocities for the next timestep
5. Use change of velocities to get coordinates for next timestep
6. Go to step 2.

$t + \Delta t$

$x(t + \Delta t)$

$v(t + \Delta t)$



Neural SHAKE Algo.

Algorithm 1 Incorporating Constraints in Diffusion Processes

Input: Initial positions of atoms $x_i^{(0)}, x_j^{(0)}$, target constraints σ_a
Output: Updated positions of atoms $x_i(t), x_j(t)$
procedure UPDATEPOSITIONS
Initialize positions according to unconstrained denoising diffusion
Set $n \leftarrow 0$
while constraints are not satisfied within tolerance **do**
$n \leftarrow n - 1$
Initial Position Update:
Update atomic positions $x_i^{(n)}(t)$ and $x_j^{(n)}(t)$ according to the unconstrained equations of motion
Matrix Formulation:
Formulate the system of equations for the Lagrange multipliers:

$$\sum_{\beta} \lambda_\beta A_{\alpha\beta}^{(n-1)}(t) = \sigma_\alpha(x(t)^{(n-1)}) \tag{7}$$

where $A_{\alpha\beta}^{(n-1)}(t) = \nabla\sigma_\alpha(x(t)^{(n-1)}) \cdot \nabla\sigma_\beta(x(t)^{(n-1)})$
Solve for Lagrange Multipliers:
Solve the system of equations to find the Lagrange multipliers λ_a
Constraint Correction:
Update atomic positions $x_i^{(n)}(t)$ as:

$$x_i^{(n)}(t) = x_i^{(n-1)}(t) - \sum_{a} \lambda_a \nabla\sigma_a(x_i(t)) \tag{8}$$

Iterative Solution:
Check if the positions converge to values that satisfy the constraints within a specified tolerance
end while
end procedure