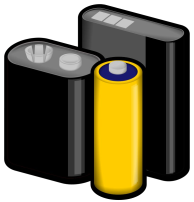
Inverse design of 3d molecular structures with conditional generative neural networks

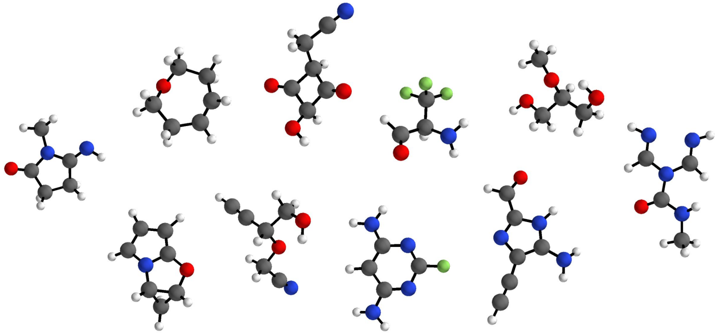
Niklas Gebauer

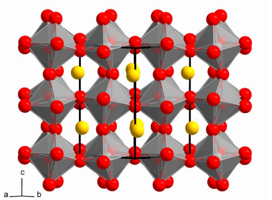
Technische Universität Berlin - Machine Learning Group

27th of February 2024

Quantum chemistry/Physics

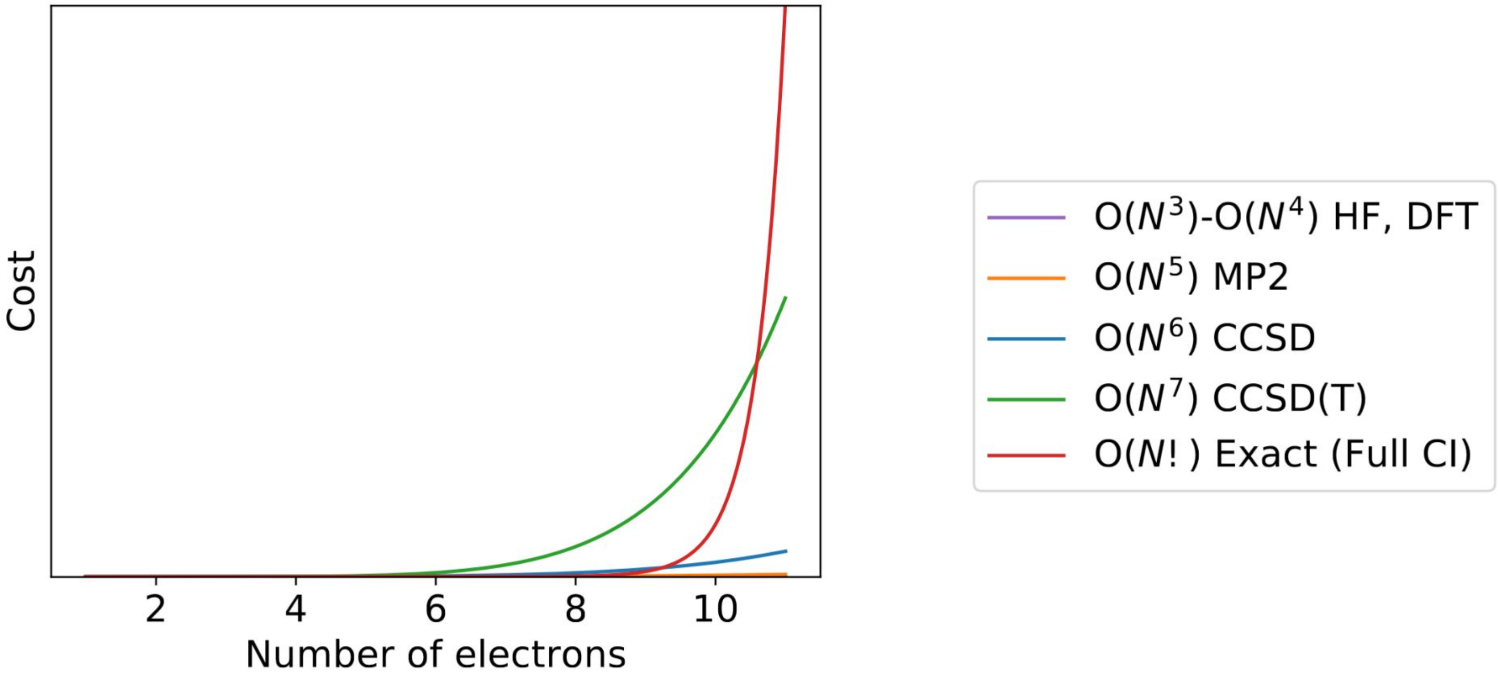




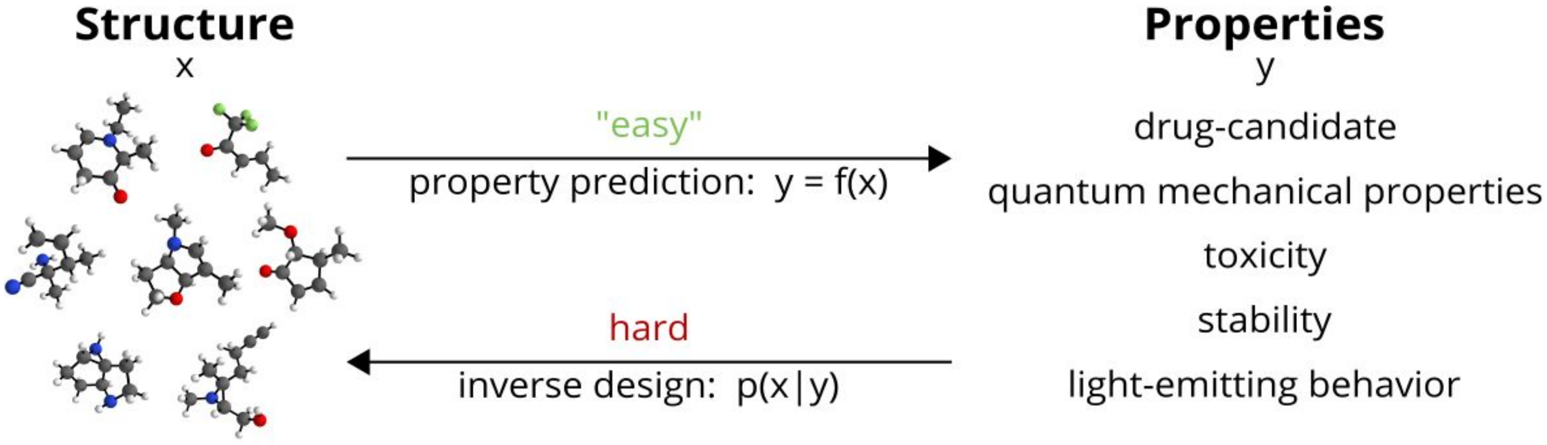


https://commons.wikimedia.org/wiki/
File:CaTiO3_perovskite_structure.png

Computational complexity of QC



ML for molecules



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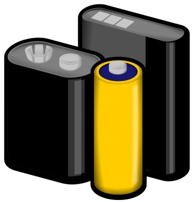
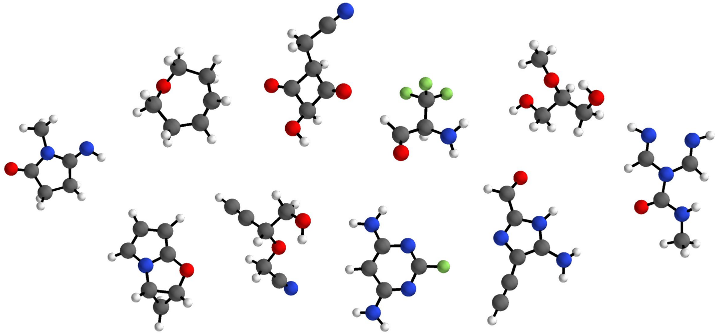
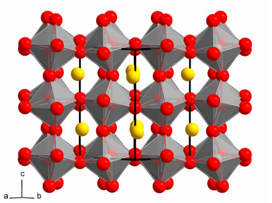


<u>guided</u> exploration of chemical space





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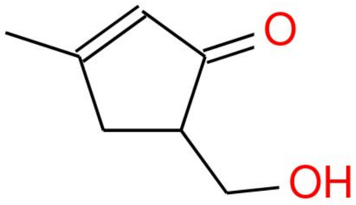
Molecule representations

SMILES strings
[Weininger 1988]

CC1=CC(=O)C(CO)C1

molecular graph



spatial

atom positions

$r_1=(x,y,z)$ $r_2=(x,y,z)$ … $r_{19}=(x,y,z)$

atom types

$Z_1=O$ $Z_2=C$ … $Z_{19}=O$

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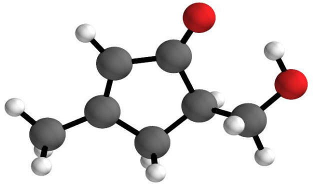

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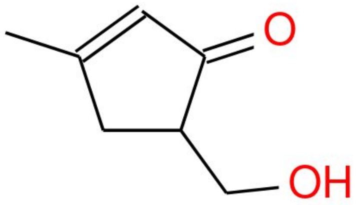

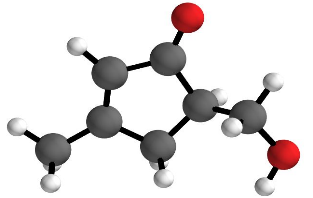

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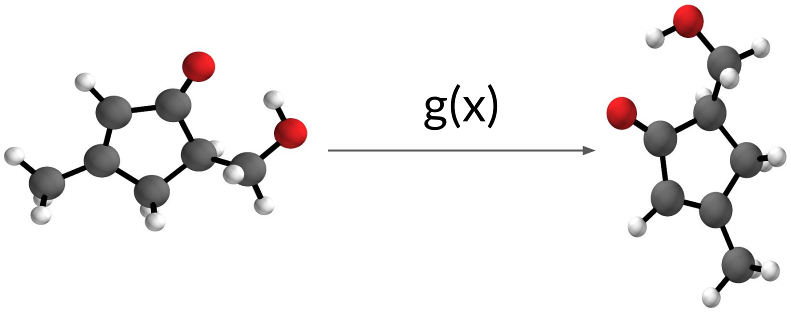
Neural network for spatial representation

- invariant networks:
  - f(g(x)) = f(x)
  - features based on pairwise distances



C O H

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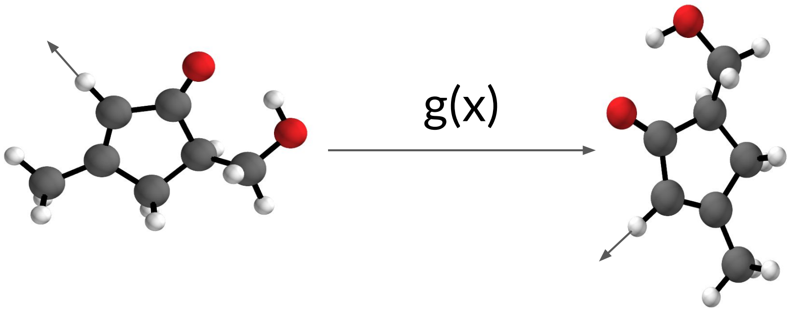
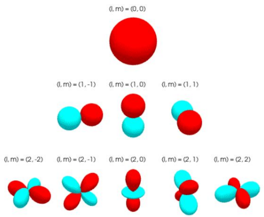


- equivariant networks:
  - f(g(x)) = g(f(x))
  - features based on direction vectors
  - specific layers required
  - spherical harmonics



https://commons.wikimedia.org/wiki/File:Real_Spherical_Harmonics_Figure_Table_Complex_Radial_Magnitude.gif

C O H

Approaches for 3d molecule generation

iterative

one-shot

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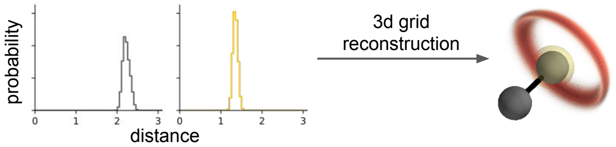
reconstruction from pairwise distances



[Gebauer et al., 2019]

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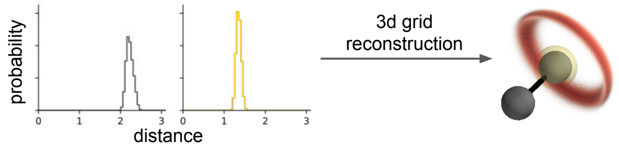

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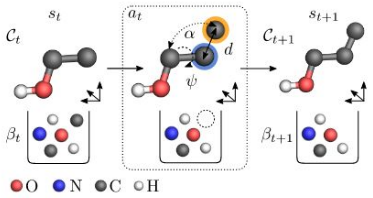

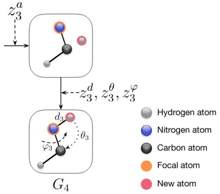

[Simm et al., 2020] [Luo & Ji, 2022]

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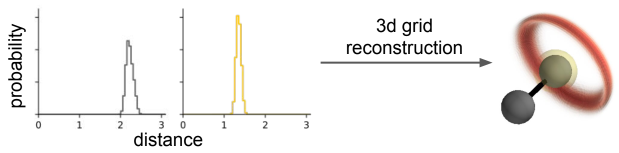

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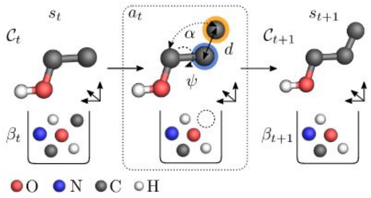

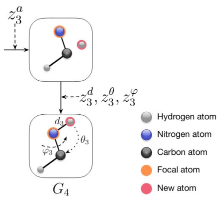

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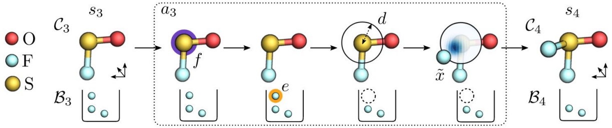
equivariant prediction of direction (spherical harmonics)



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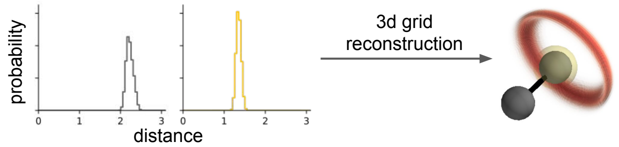

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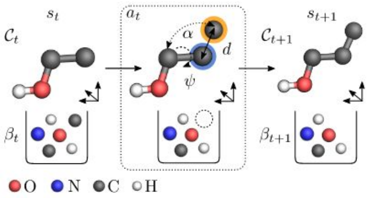

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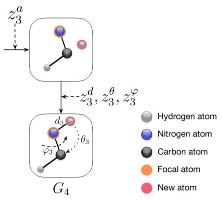

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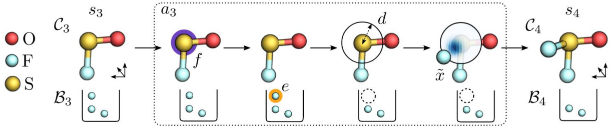
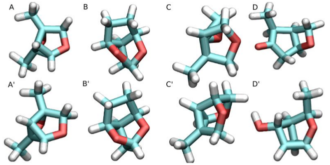


[Simm et al., 2021]

one-shot

generating valid euclidean distance matrices



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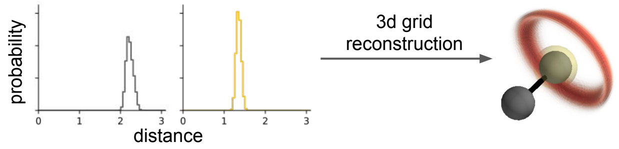

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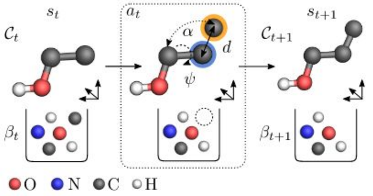

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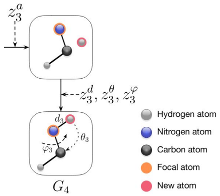

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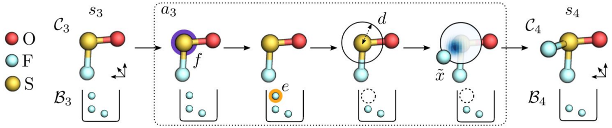

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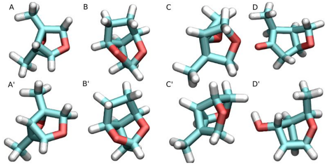

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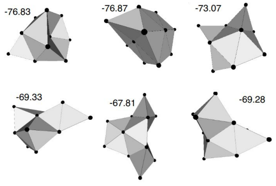
equivariant normalizing flow



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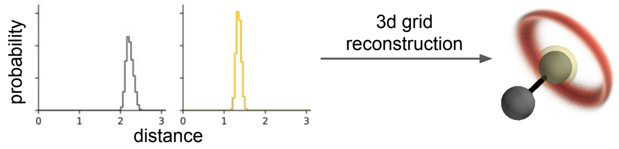

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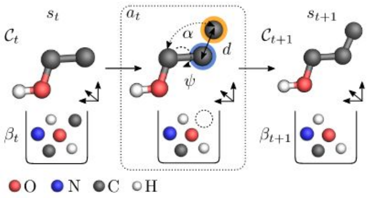

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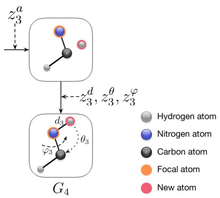

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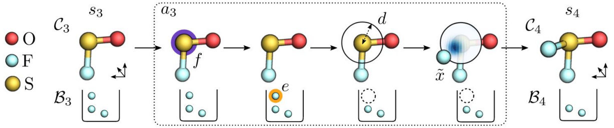

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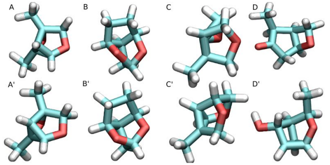

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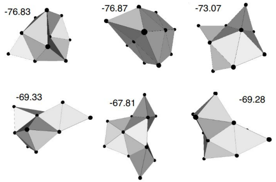

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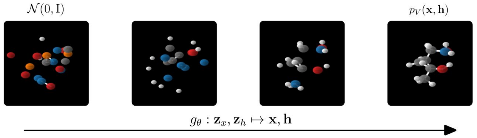

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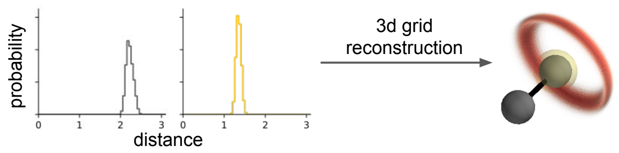

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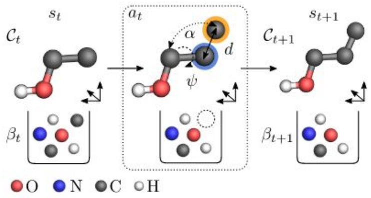

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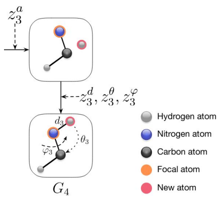

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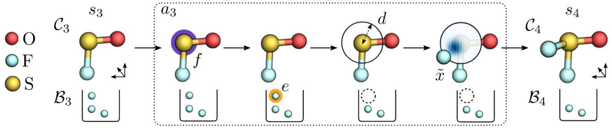

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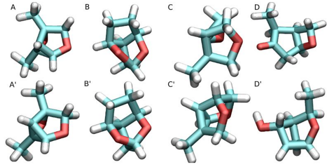

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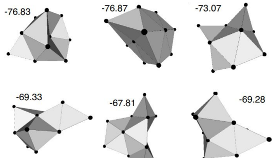

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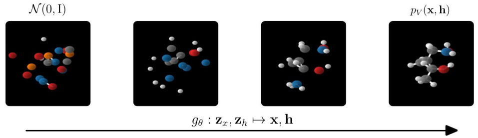

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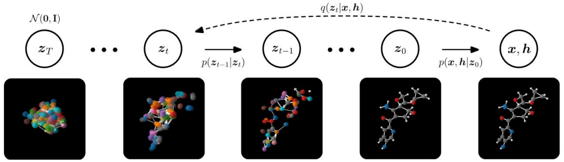
equivariant diffusion



[Hoogeboom et al., 2022]

Autoregressive approach

$$p(\mathbf{r}_1, ..., \mathbf{r}_n, Z_1, ..., Z_n) = \prod_{i=0}^{n-1} p(\mathbf{r}_{i+1}, Z_{i+1} | \mathbf{r}_1, ..., \mathbf{r}_i, Z_1, ..., Z_i)$$

Deep
Neural
Network

G-SchNet

[Gebauer et al., 2019]

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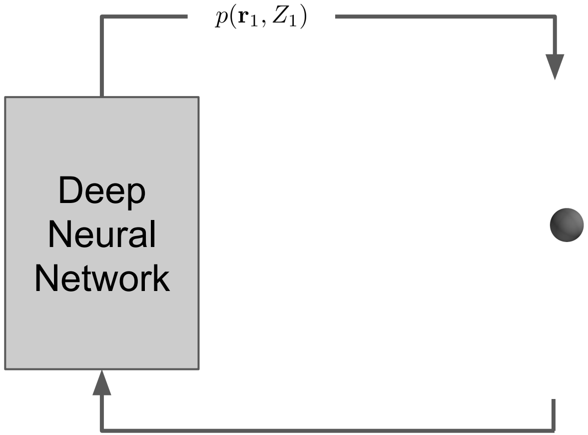

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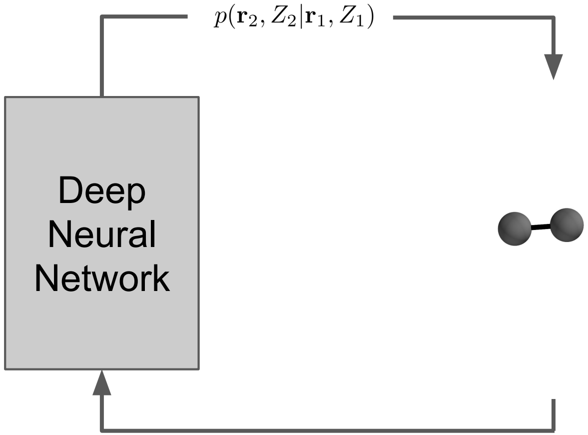

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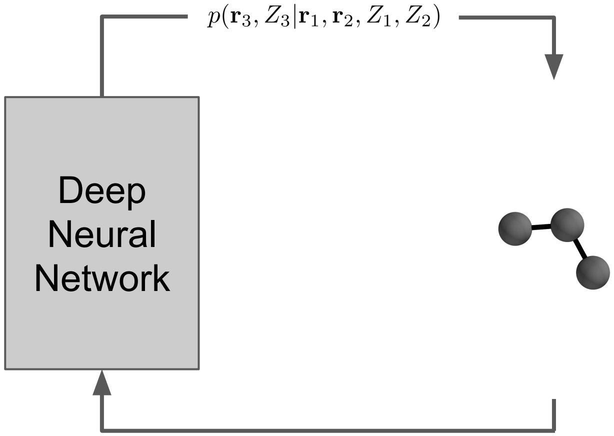

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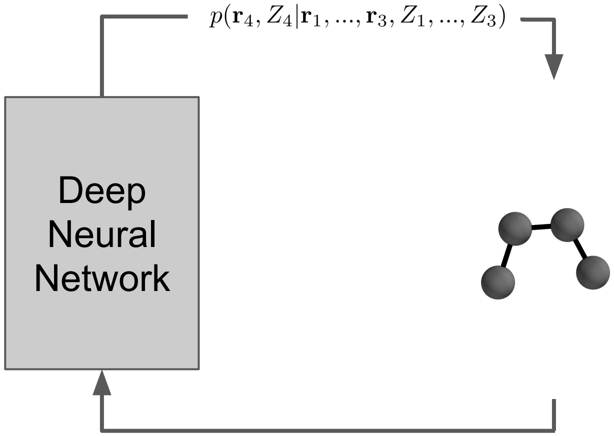

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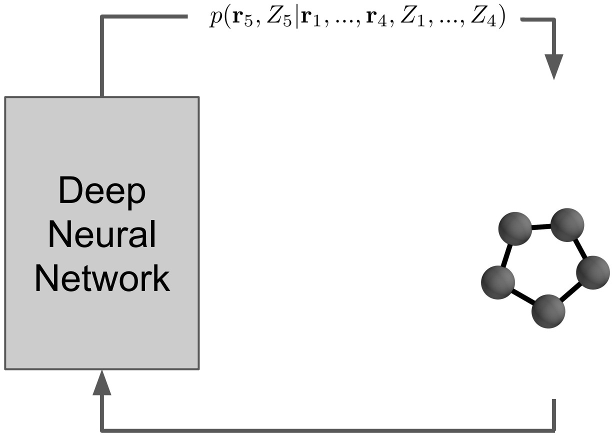

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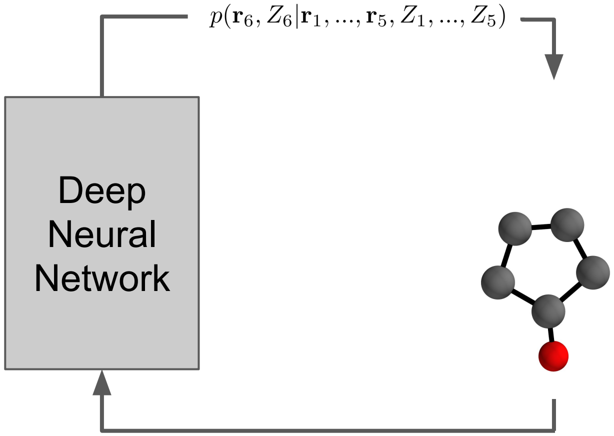

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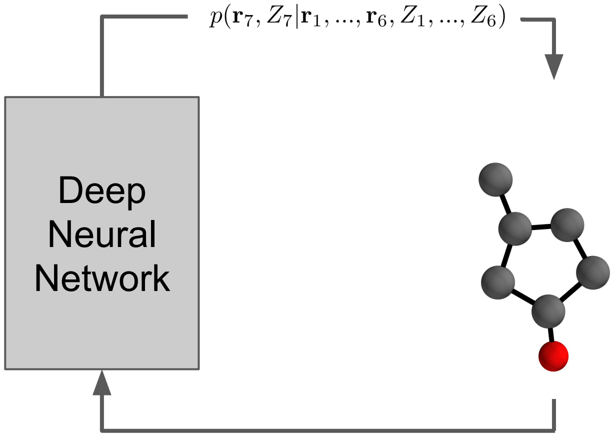

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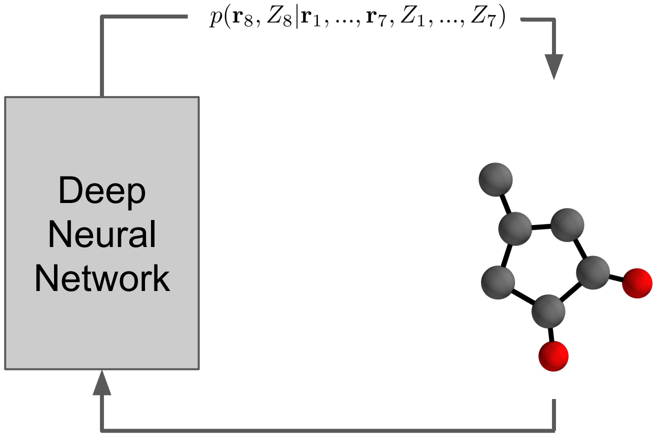

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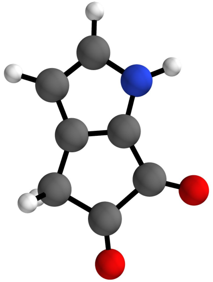
[Gebauer et al., 2019]

Autoregressive approach

$$p(\mathbf{r}_1, ..., \mathbf{r}_n, Z_1, ..., Z_n) = \prod_{i=0}^{n-1} p(\mathbf{r}_{i+1}, Z_{i+1} | \mathbf{r}_1, ..., \mathbf{r}_i, Z_1, ..., Z_i)$$

Deep
Neural
Network



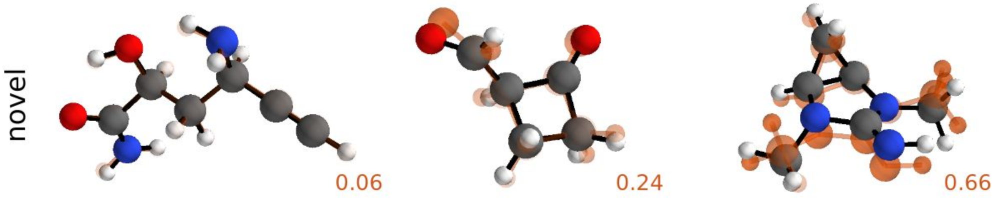
G-SchNet

[Gebauer et al., 2019]

Autoregressive approach

$$p(\mathbf{r}_1, ..., \mathbf{r}_n, Z_1, ..., Z_n) = \prod_{i=0}^{n-1} p(\mathbf{r}_{i+1}, Z_{i+1} | \mathbf{r}_1, ..., \mathbf{r}_i, Z_1, ..., Z_i)$$

Deep Neural Network



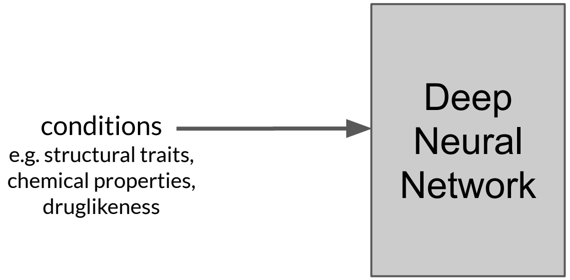
- sampling of valid, stable small organic molecules
- captures characteristics of the training data

G-SchNet

[Gebauer et al., 2019]

Autoregressive approach - conditional

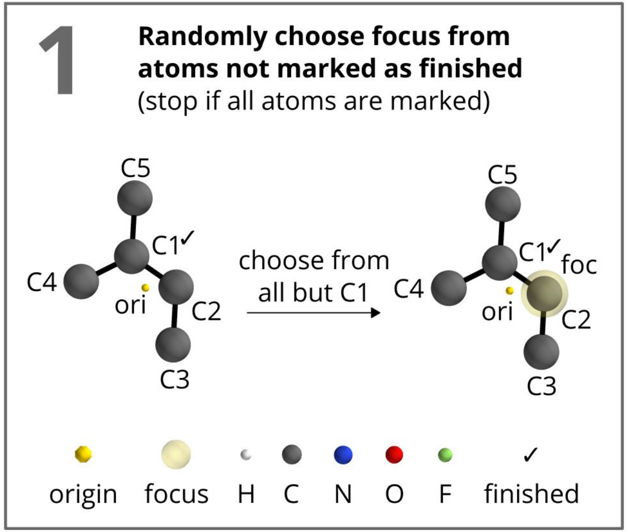
$$p(\mathbf{r}_1, ..., \mathbf{r}_n, Z_1, ..., Z_n | \lambda_1, ..., \lambda_k) = \prod_{i=0}^{n-1} p(\mathbf{r}_{i+1}, Z_{i+1} | \mathbf{r}_1, ..., \mathbf{r}_i, Z_1, ..., Z_i, \lambda_1, ..., \lambda_k)$$



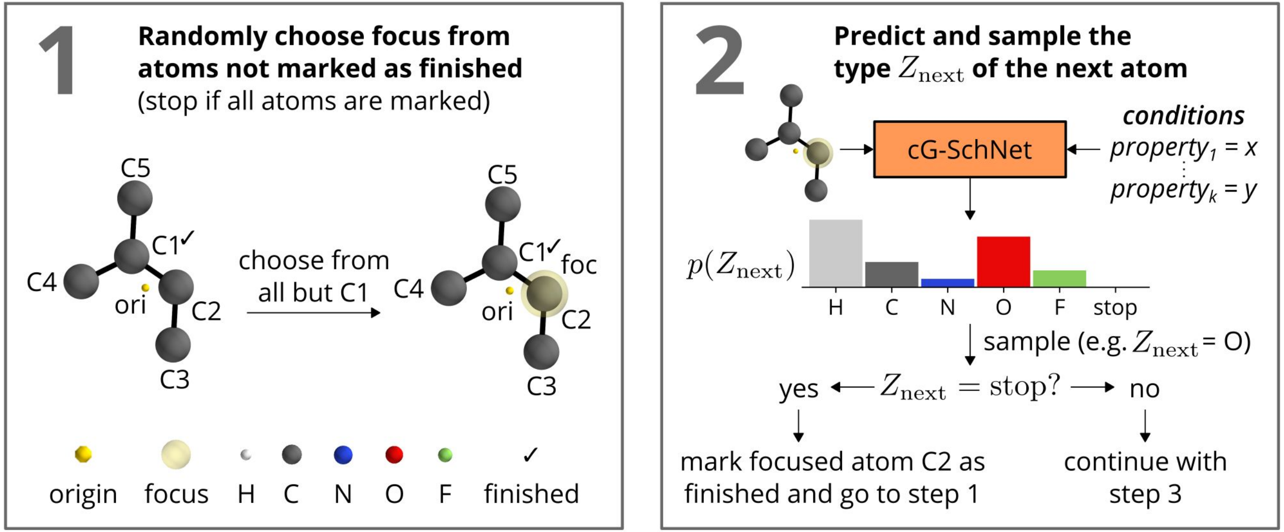
cG-SchNet

[Gebauer et al., 2022]

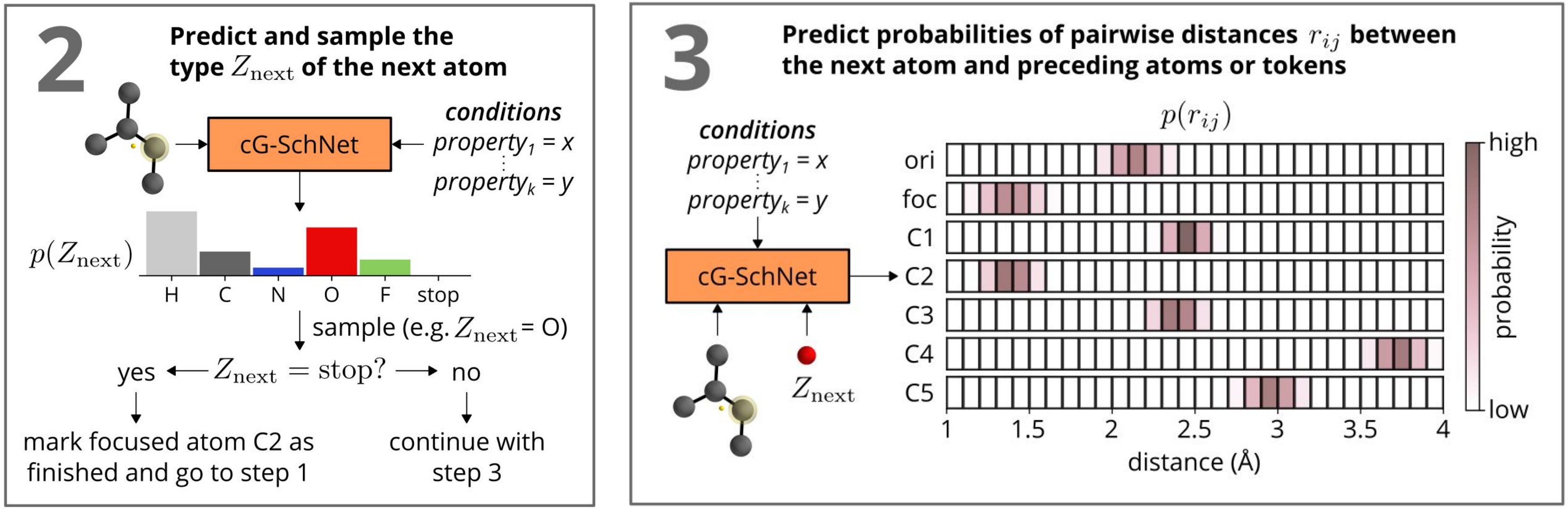
Atom placement loop with cG-SchNet



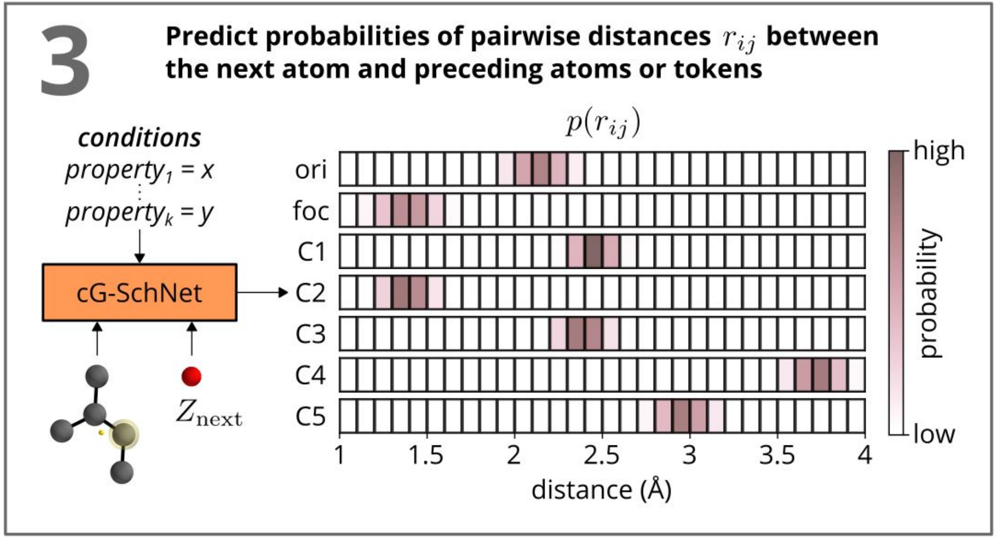
Atom placement loop with cG-SchNet

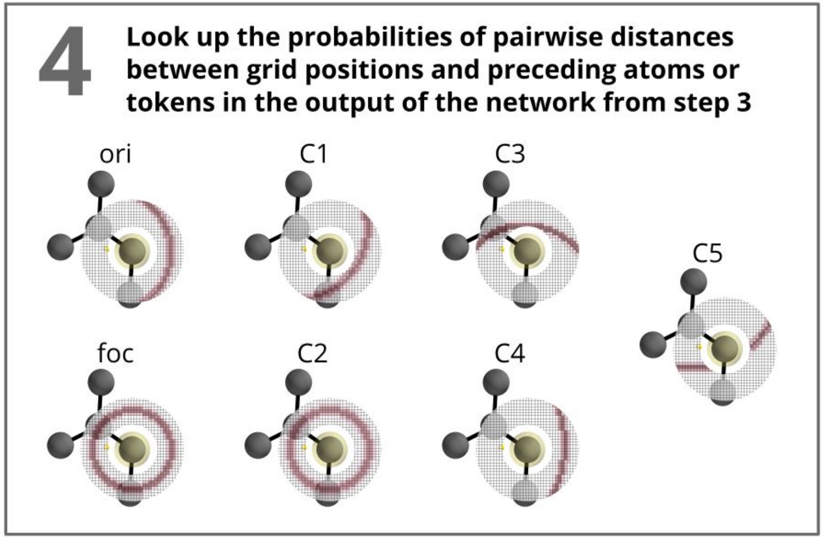


Atom placement loop with cG-SchNet



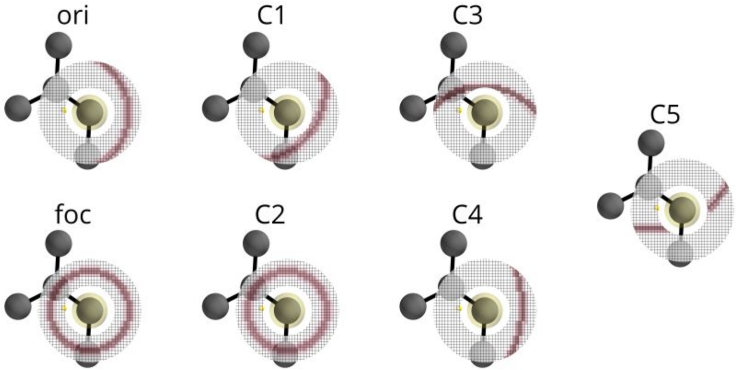
Atom placement loop with cG-SchNet





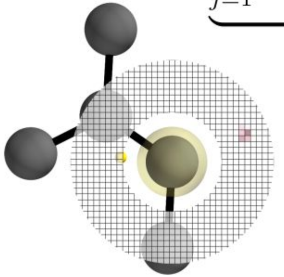
Atom placement loop with cG-SchNet

4 **Look up the probabilities of pairwise distances between grid positions and preceding atoms or tokens in the output of the network from step 3**



5 **Multiply probabilities at each position to reconstruct a distribution for the position $\mathbf{r}_{\text{next}}$ of the next atom**

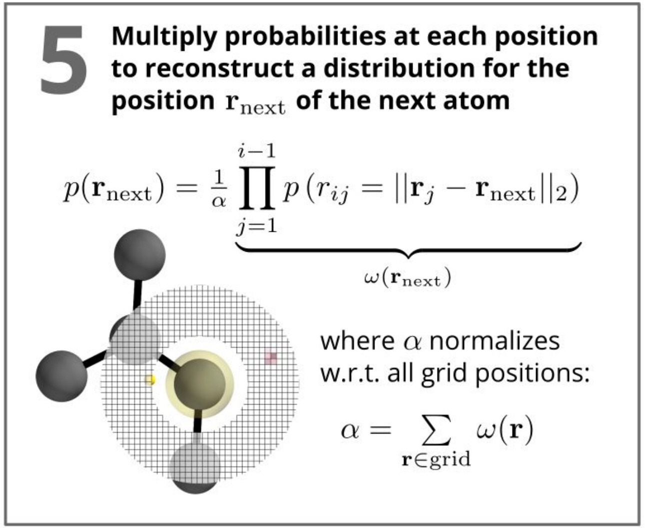
$$p(\mathbf{r}_{\text{next}}) = \frac{1}{\alpha} \underbrace{\prod_{j=1}^{i-1} p\left(r_{ij} = ||\mathbf{r}_j - \mathbf{r}_{\text{next}}||_2\right)}_{\omega(\mathbf{r}_{\text{next}})}$$

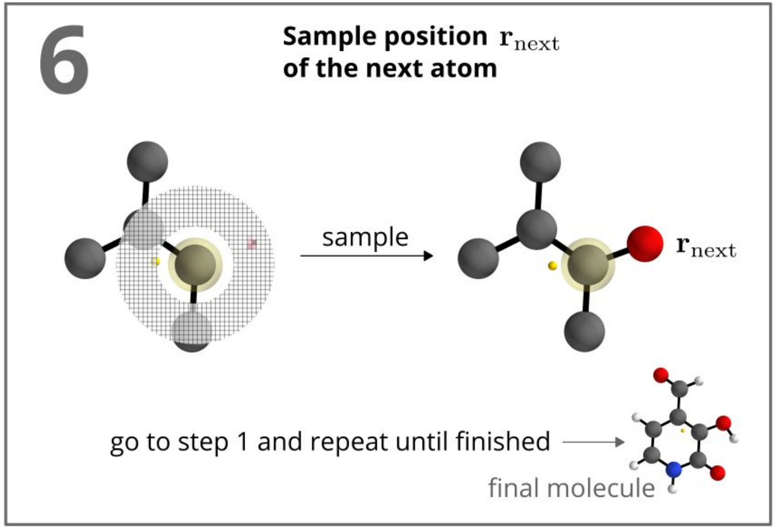


where α normalizes w.r.t. all grid positions:

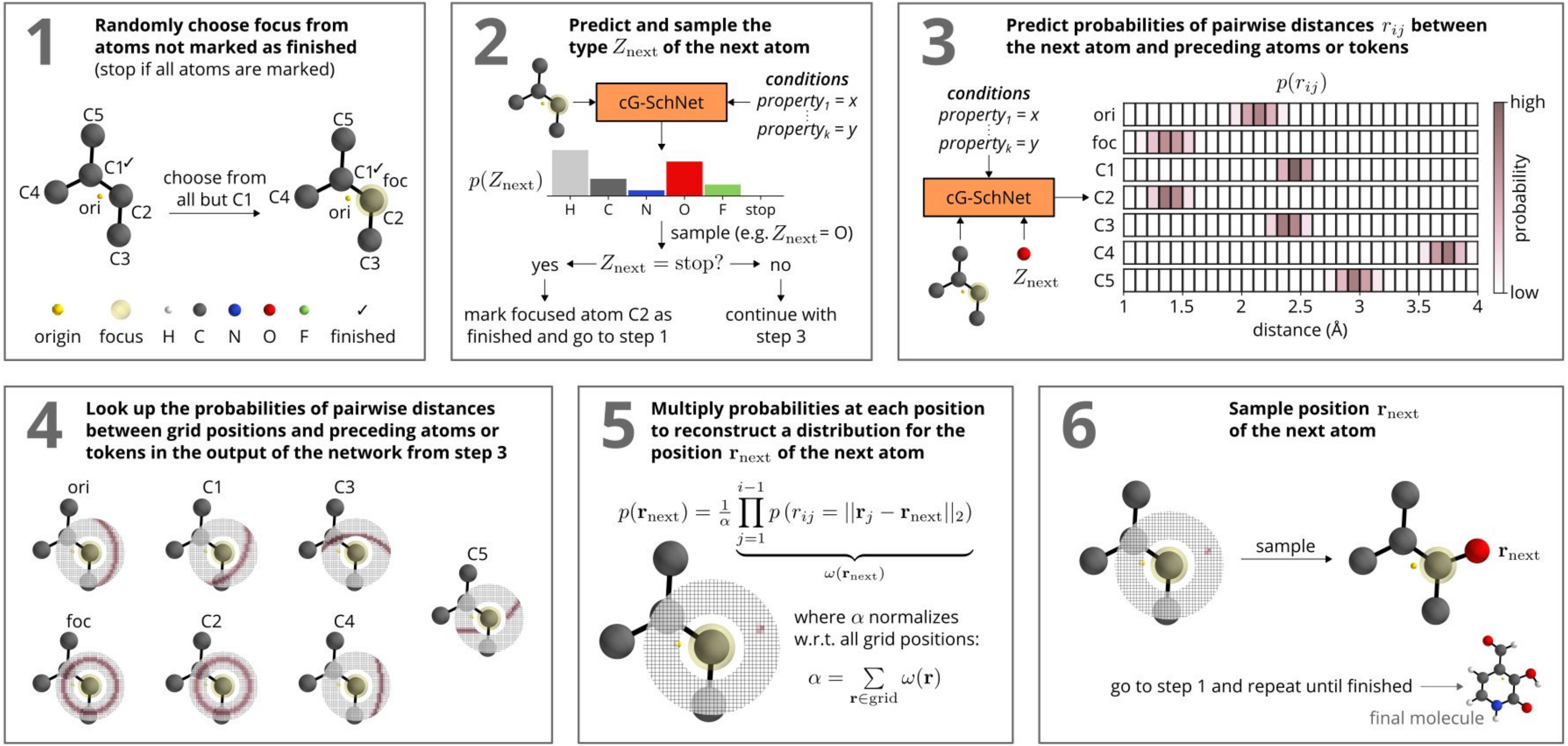
$$\alpha = \sum_{\mathbf{r}\in\text{grid}} \omega(\mathbf{r})$$

Atom placement loop with cG-SchNet

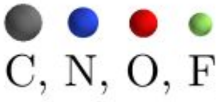




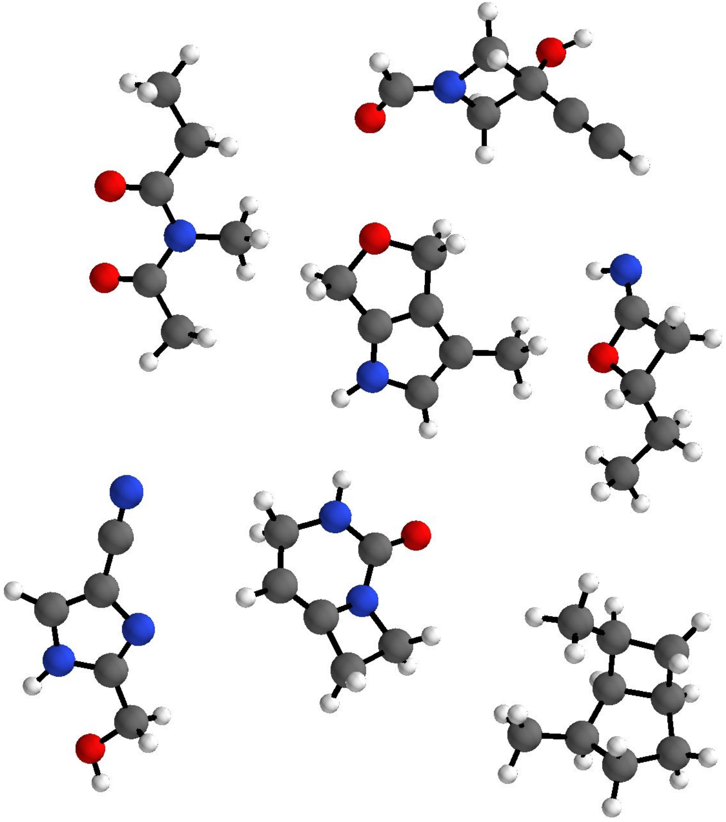
Atom placement loop with cG-SchNet



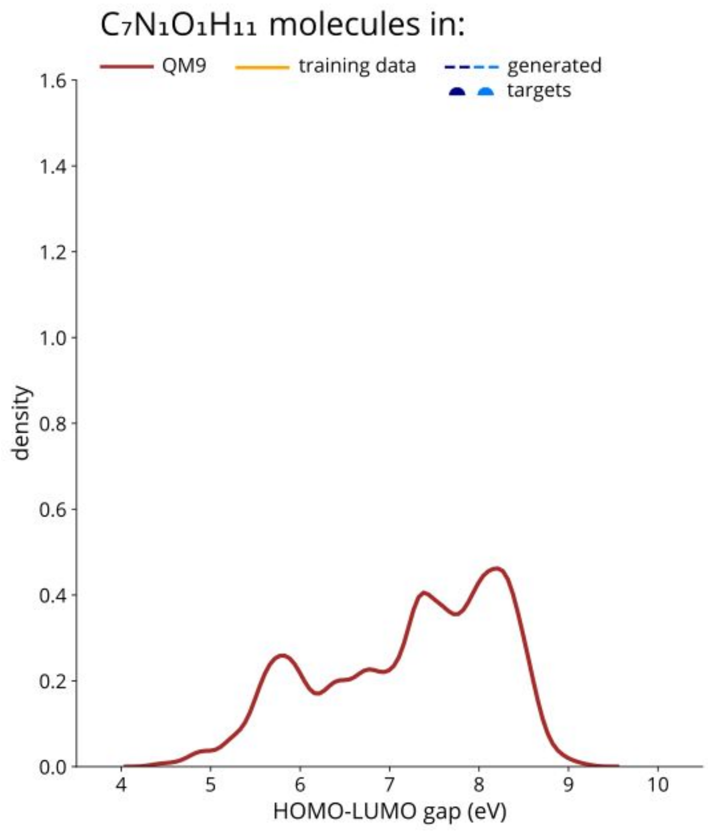
QM9

- ~130k stable molecules
- up to 9 heavy atoms 

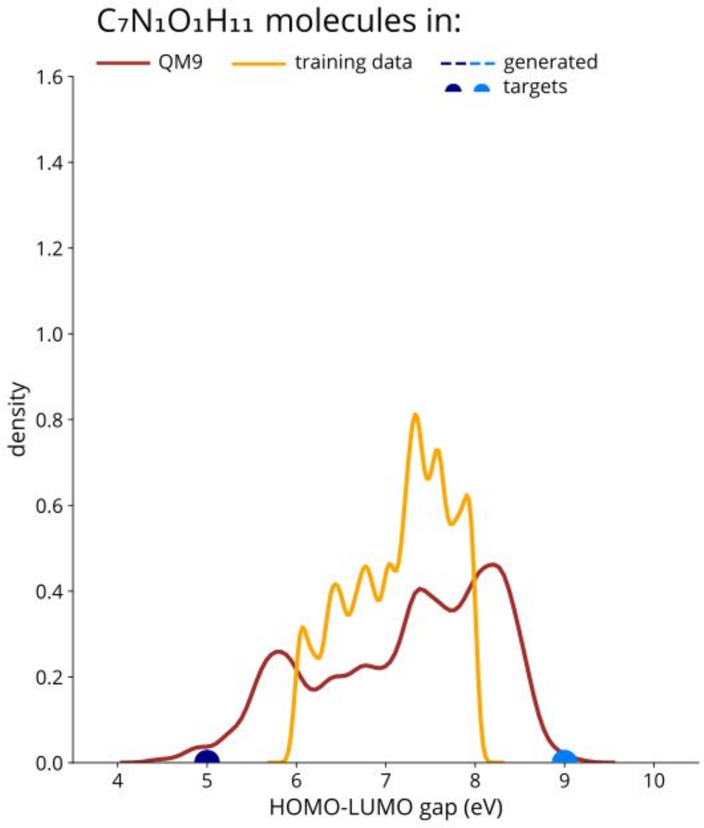
- 55k for training



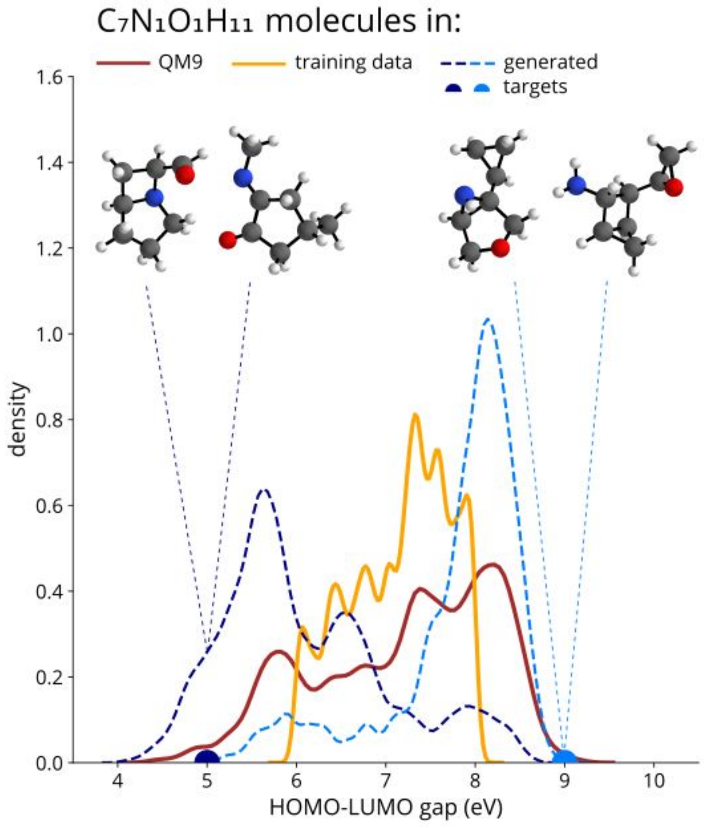
Results: Generalization across compositions



Results: Generalization across compositions



Results: Generalization across compositions



Challenges

- no real-world success story yet
- limited data availability
  - benchmark data sets have no practical applications
  - more interesting data owned by companies
  - data costly to compute
- mostly applied to:
  - small structures
  - non-periodic systems
- targeting many properties is difficult

Conclusion

- diverse applications require guided exploration of chemical space
- cG-SchNet for the conditional generation of 3d molecules
  - deep neural network respecting local and global symmetries
  - generates stable molecules capturing statistics of the training data
  - generalizes to unseen conditions to sample target-dependent candidates
  - allows for data-efficient, guided exploration of small organic compounds
- generative models for 3d structures are gaining traction
  - ignoring spatial component is a limiting factor
  - data availability is comparatively bad
  - models are still limited

➢ increase focus on targeted exploration (conditioning/biasing)

➢ application to crystal structures and larger molecules

Thank you!

Questions?

Literature

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