Generative Models for Structured Based Drug Design

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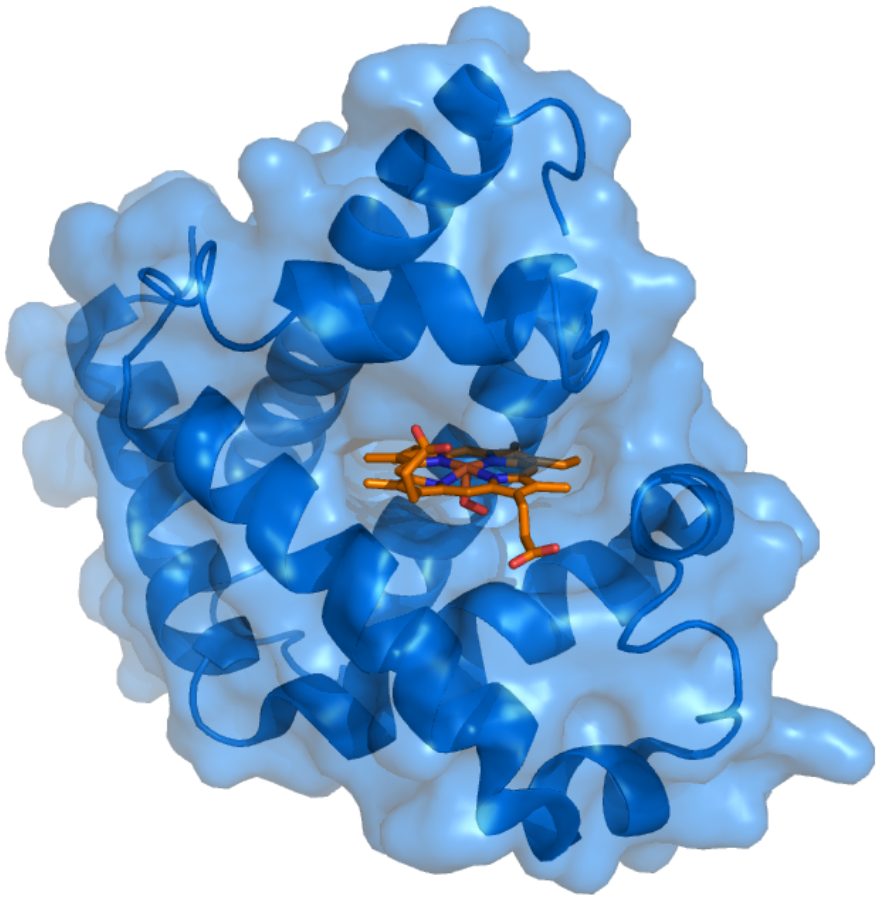
Structured Based Drug Design (SBDD)

Drug design: Find a small molecule(ligand) that binds to a specific protein, modulating its function

SBDD: Exploit the 3D structure of the protein to design drugs



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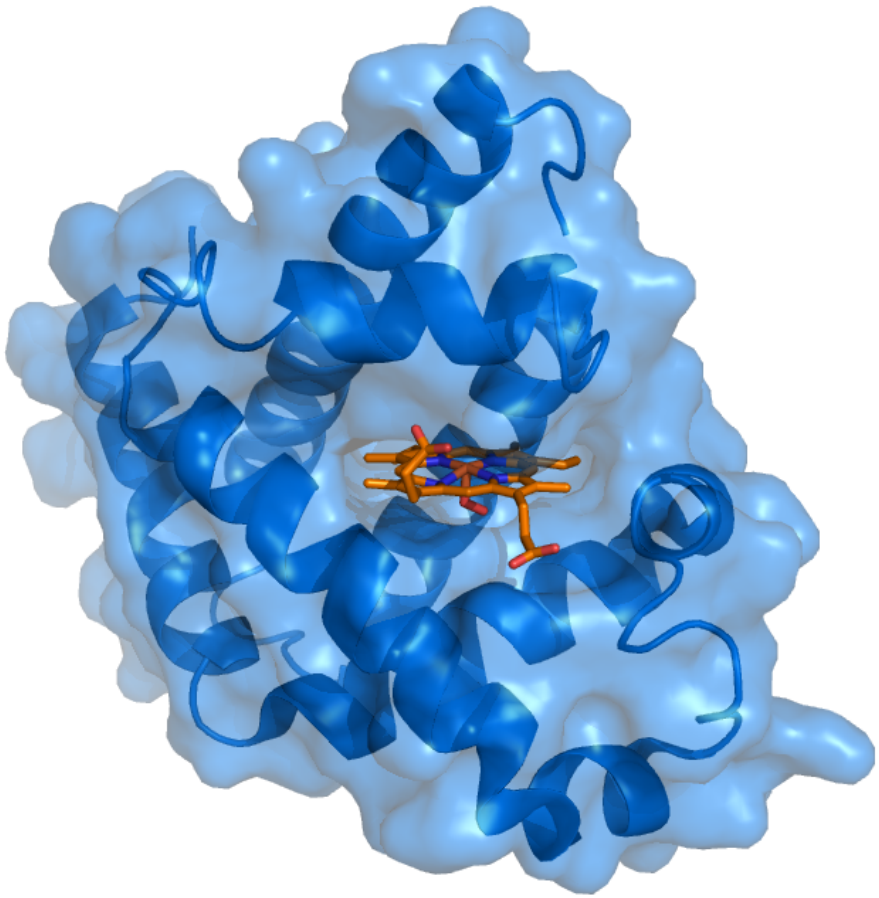

Traditional methods:

- Insufficient exploration of the *enormous* chemical space
- Huge cost

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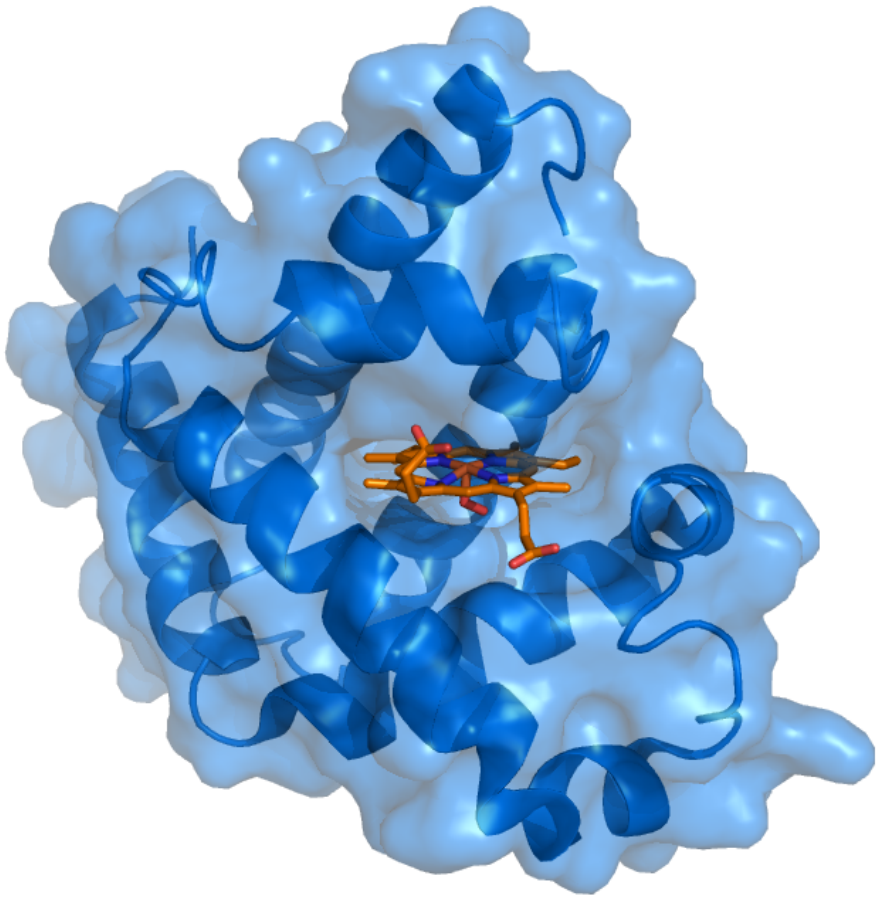

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Idea: Use generative models!

Deep Generative Models - Creating new data

panda mad scientist mixing sparkling chemicals, artstation

Basic idea:
Learn the distribution of the data and then sample from it

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Figure taken from [8]

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Learn the distribution of the data and then sample from it

For SBDD:
Capture the conditional distribution of a ligand forming a complex with a given protein

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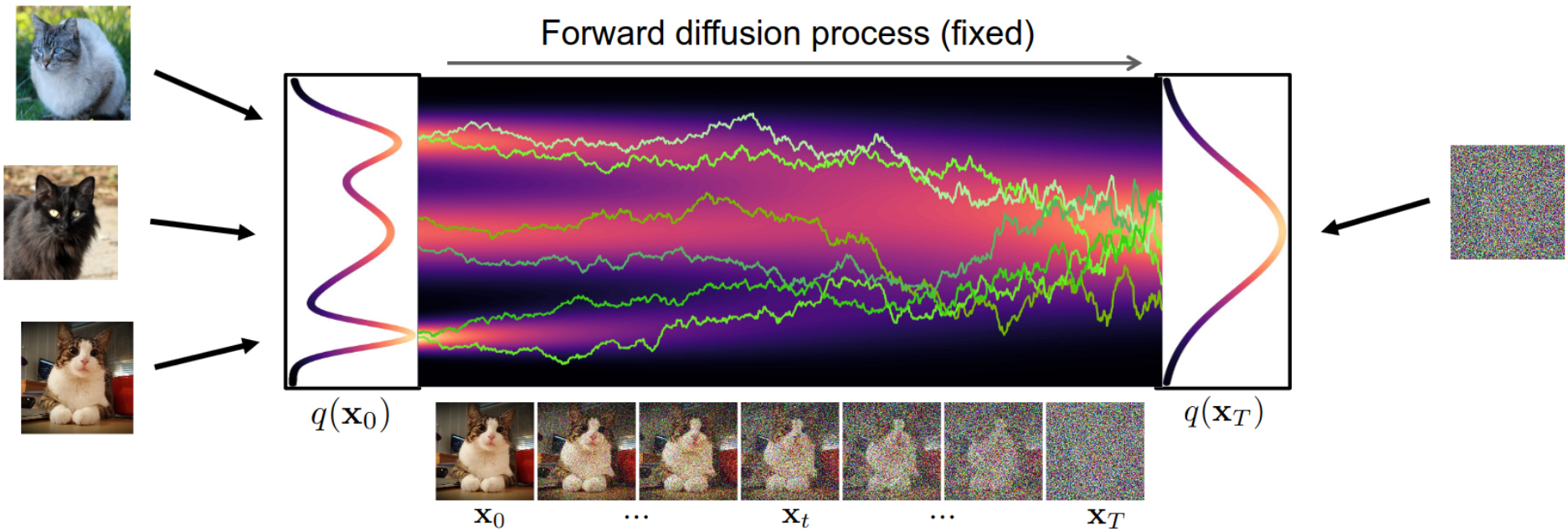
Diffusion Models - Generating data from noise

- **Forward process:** Add noise gradually $\rightarrow$ pure noise at the end
- **Backward process:** A Neural Network learns to reconstruct the original data
- **Generation:** Sample pure noise and use the backward process



Ho et al., Denoising diffusion probabilistic models. NeurIPS, 2020
Figure taken from [14]

Graph Neural Networks - Operating on molecules

- Molecules are graphs $\rightarrow$ **GNNs**

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- Molecules are graphs $\rightarrow$ **GNNs**
- Vanilla GNNs are not enough $\rightarrow$ We need **equivariance**

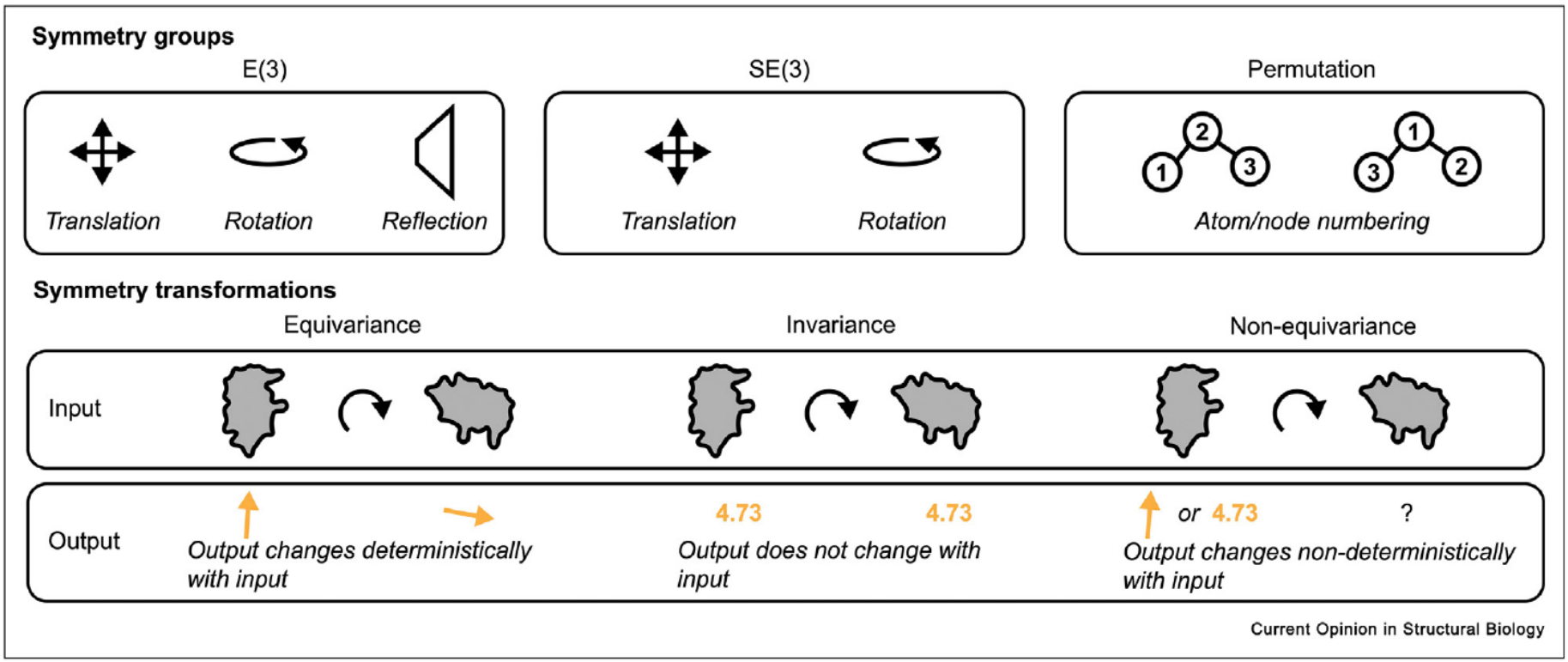

Figure taken from [1]

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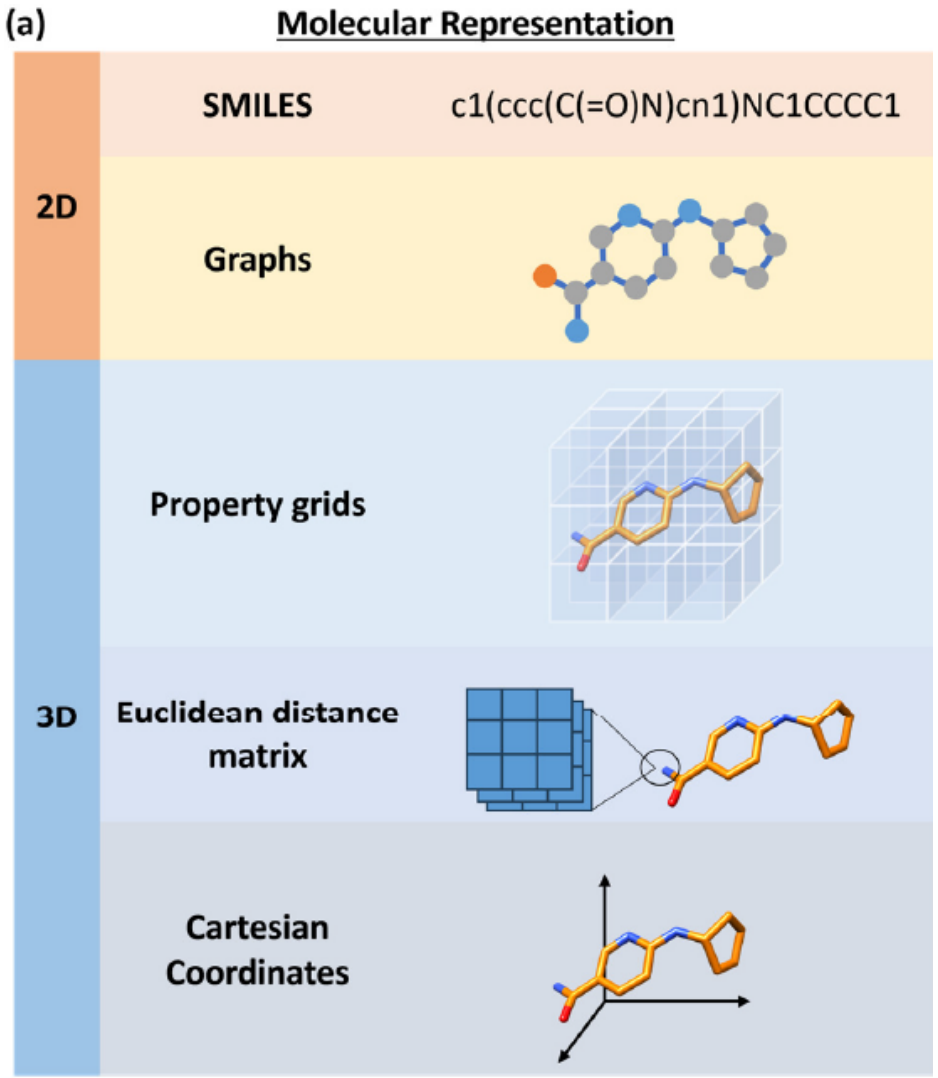
Choosing a representation



- **2D/1D representations:** Convert molecules to strings (e.g SMILES), use sequence-based models like RNNs, Transformers [10,16,17]

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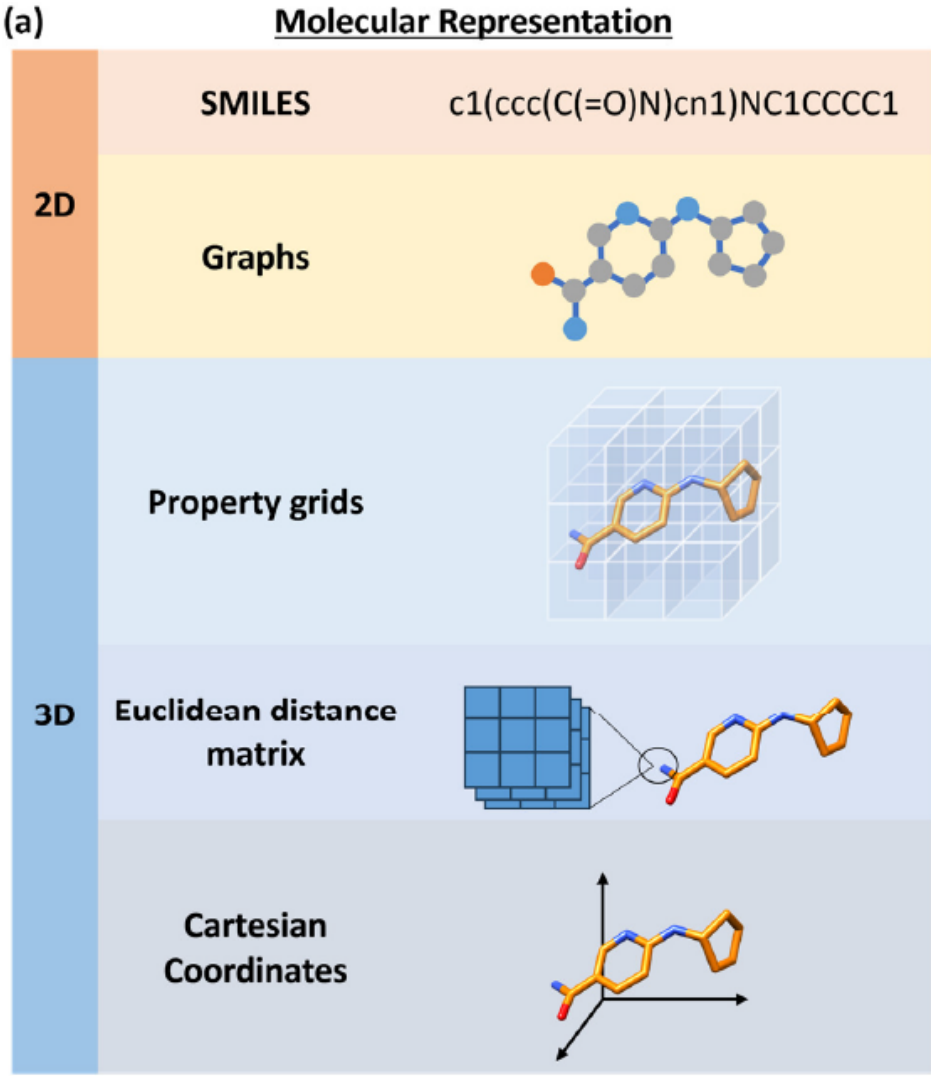
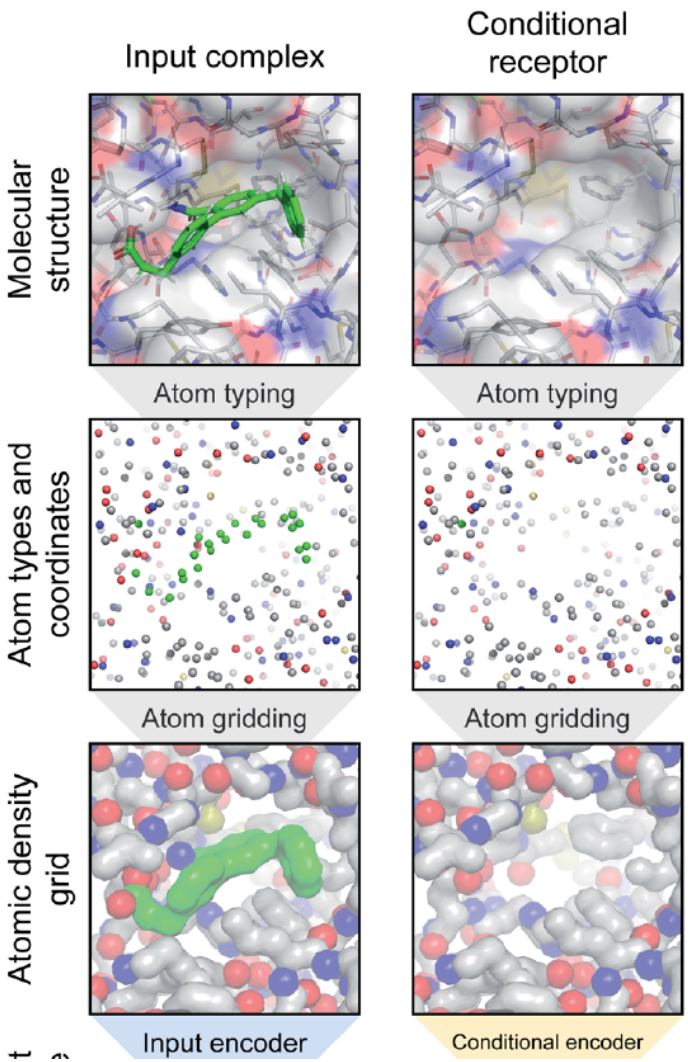


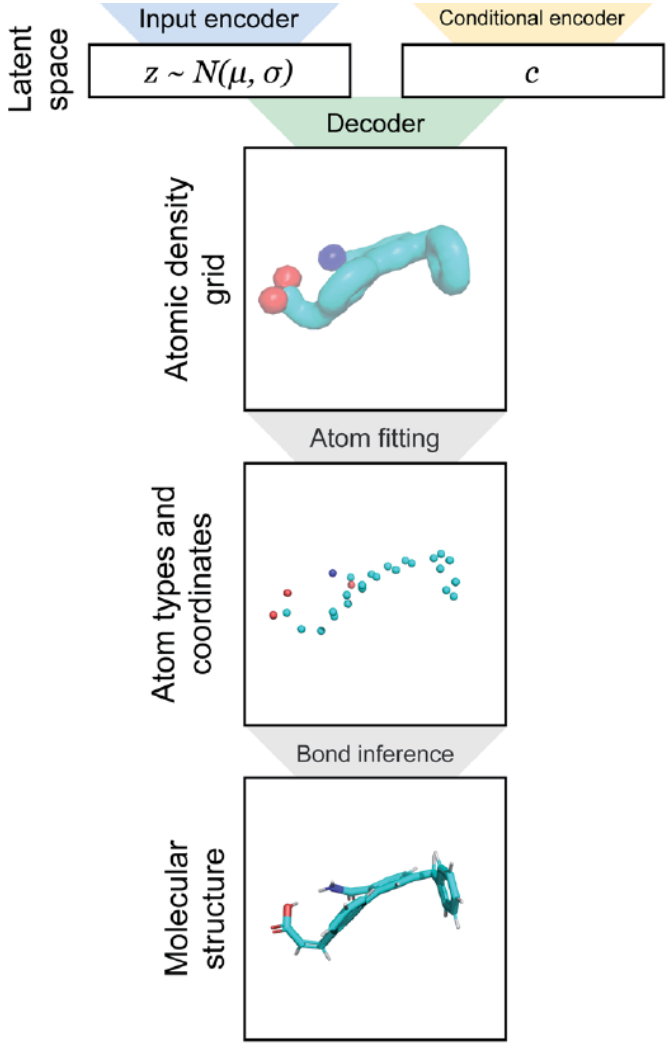
Figure taken from [7]

- **2D/1D representations:** Convert molecules to strings (e.g SMILES), use sequence-based models like RNNs, Transformers [10,16,17]
- **3D representations:** Explicitly model the 3D structure of the molecule

Grid-based models - liGAN



(a)



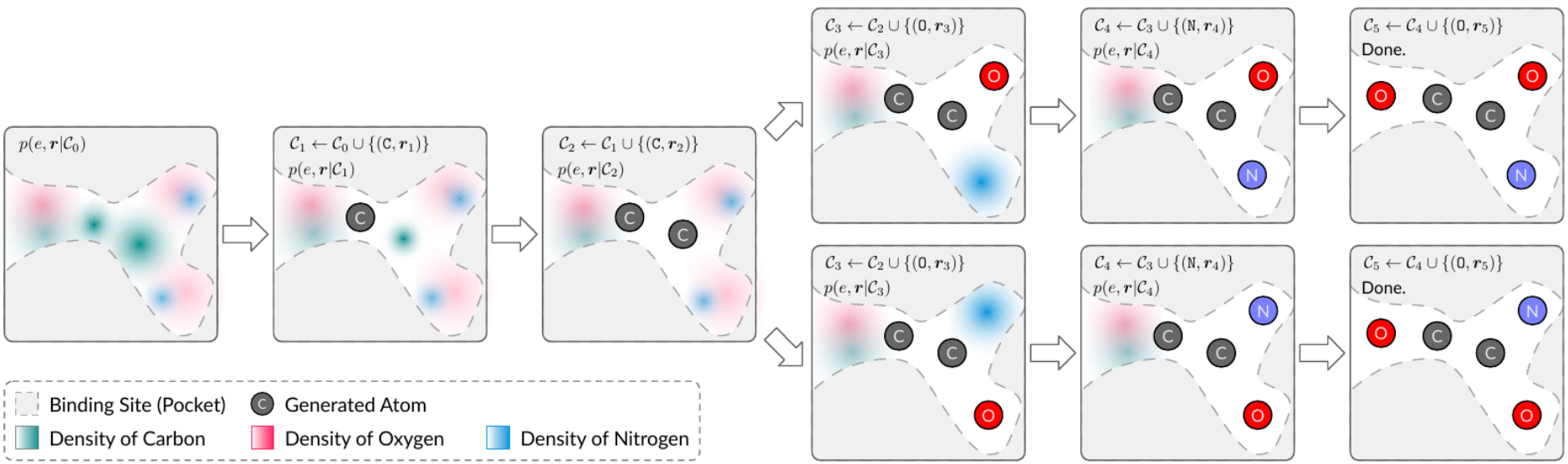
(b)

Ragoza et. al, Generating 3D molecules conditional on receptor binding sites with deep generative models, Chemical Science 2022

Autoregressive models - Luo et. al

Main ideas:

- Model the density $p(e, r|\mathcal{C}_0)$
- Sample atoms one by one
- Rotation/Translation invariant GNNs for **context encoding**
- A **spatial classifier** estimates the probability of finding an atom of type e at position r

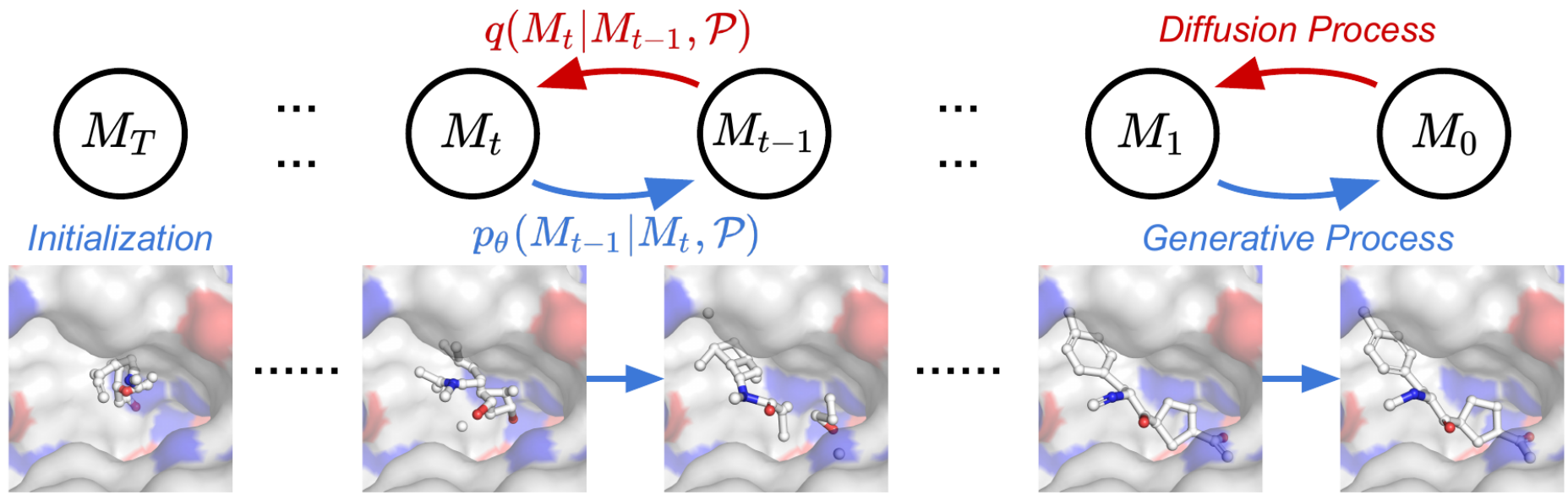


Luo et. al, A 3D Generative Model for Structure-Based Drug Design. NeurIPS 2021

Diffusion models - TargetDiff

Main ideas:

- Diffusion model, invariant likelihood for SE(3) transformations
- Equivariant GNNs for the denoising process
- Diffusion on both positions and atom types, protein remains fixed

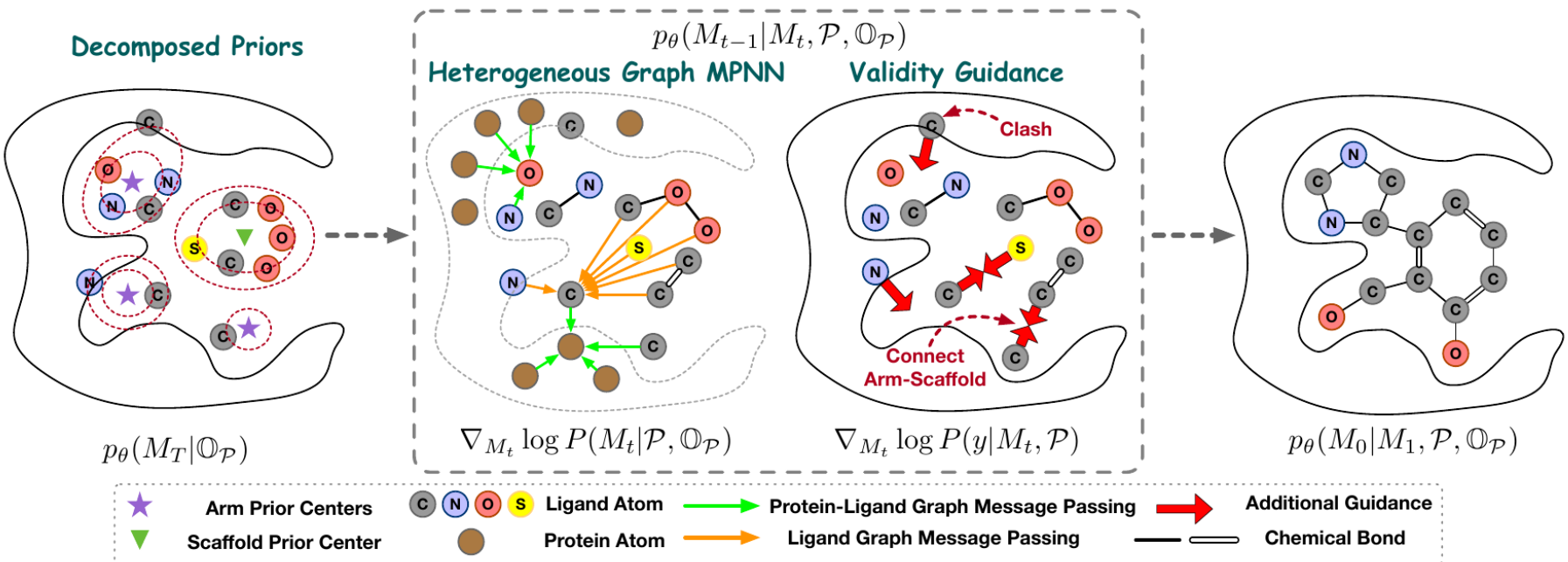


Guan et al, 3D Equivariant Diffusion for Target-Aware Molecule Generation and Affinity Prediction, ICLR 2023

Diffusion models - DecompDiff

Main ideas:

- Equivariant diffusion model
- Decomposed priors over *arms* and *scaffold*
- Both atom and bond diffusion
- Validity guidance



Guan et al., DecompDiff: Diffusion models with Decomposed Priors for Structure-Based Drug Design, ICML 2023

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Evaluation metrics - Results

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- Vina Score $\rightarrow$ Binding affinity
- QED $\rightarrow$ Drug-likeness
- SA $\rightarrow$ Synthetic accessibility
- Diversity

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Data sets

CrossDocked [11], synthetically generated dataset

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Data sets

CrossDocked [11], synthetically generated dataset

Method	Vina Score	QED	SA	Diversity
liGAN	-6.33	0.39	0.59	0.66
Luo et al	-6.75	**0.51**	**0.63**	0.70
TargetDiff	-7.80	0.48	0.58	**0.72**
DecompDiff	**-8.39**	0.45	0.61	0.68

Discussion

Current issues:

- Not easy to compare 1D and 3D methods
- Need for a comprehensive evaluation framework for SBDD
- Experimental validation
- Both datasets and evaluation metrics are limited by score functions

Outlook: Close collaboration between domains experts and ML researchers, to combine state-of-the-art methods with domain-specific knowledge

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Thank you for your attention!