Summer School Lab

Molecular Generation

June 14, 2024

Presented by

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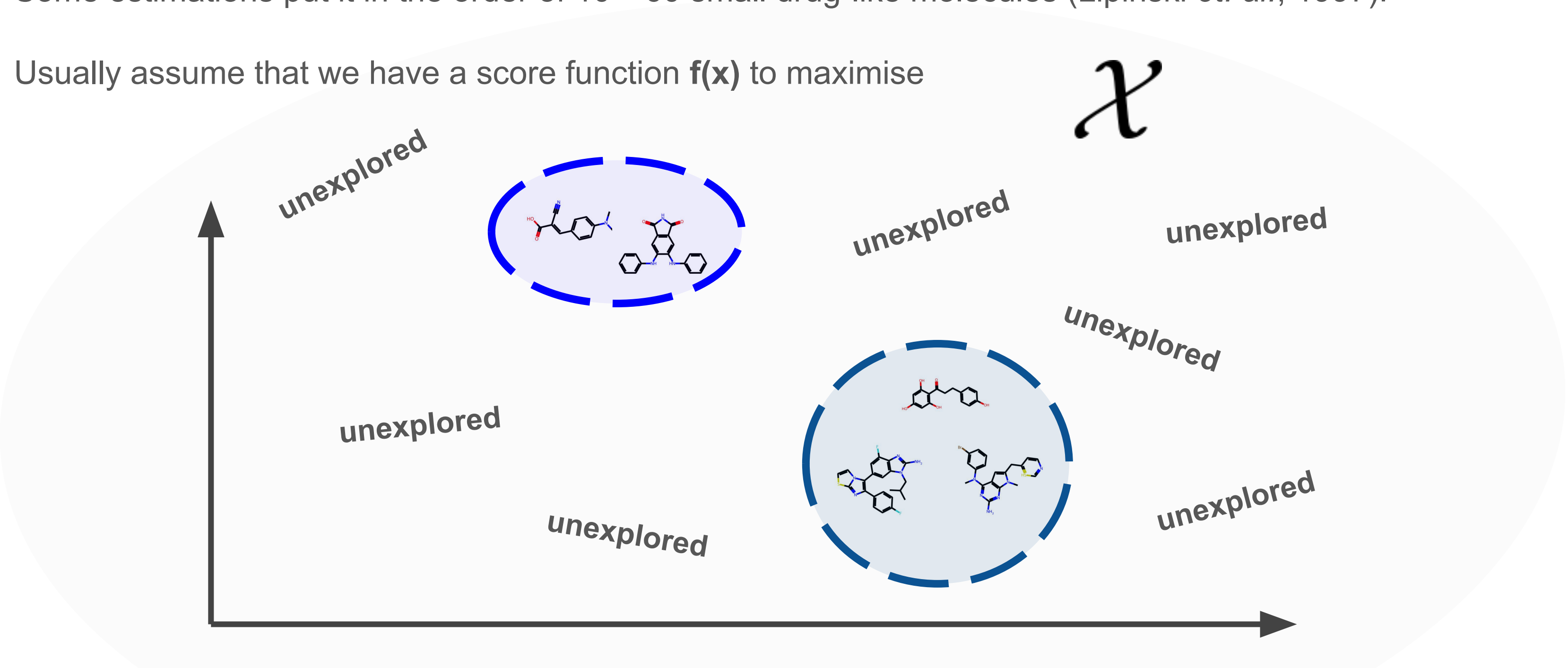
Agenda

15:00 - 15:30	**Graph GA**
15:30 - 16:00	Break
16:00 - 16:45	**Fragment GFlowNet**
16:45 - 17:15	**SAFE Scaffold Decoration**
17:15 - 17:30	Recap

Motivation

- **The Molecular Space is vast**
  It contains all the molecules that have ever been manufactured, and all the molecules that *could* exist !
  Some estimations put it in the order of 10 ^ 60 small drug-like molecules (Lipinski *et. al.*, 1997).

- Usually assume that we have a score function **f(x)** to maximise



Genetic Algorithms for molecular generation

- **Iterative application of selection and mutation steps**

  Selection: select the members of the population (molecule) with the highest fitness (score)

  Mutation: combine different elements of the population members to create the next generation

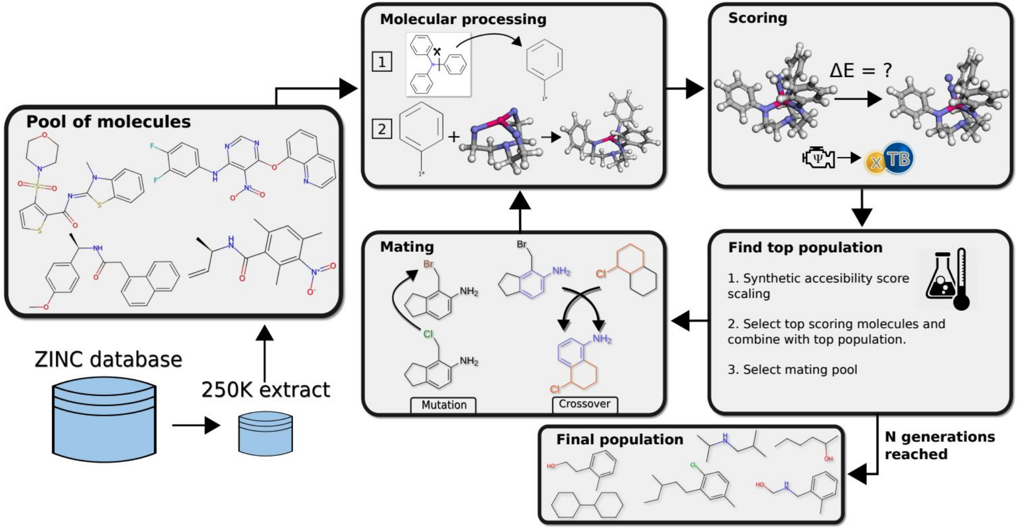
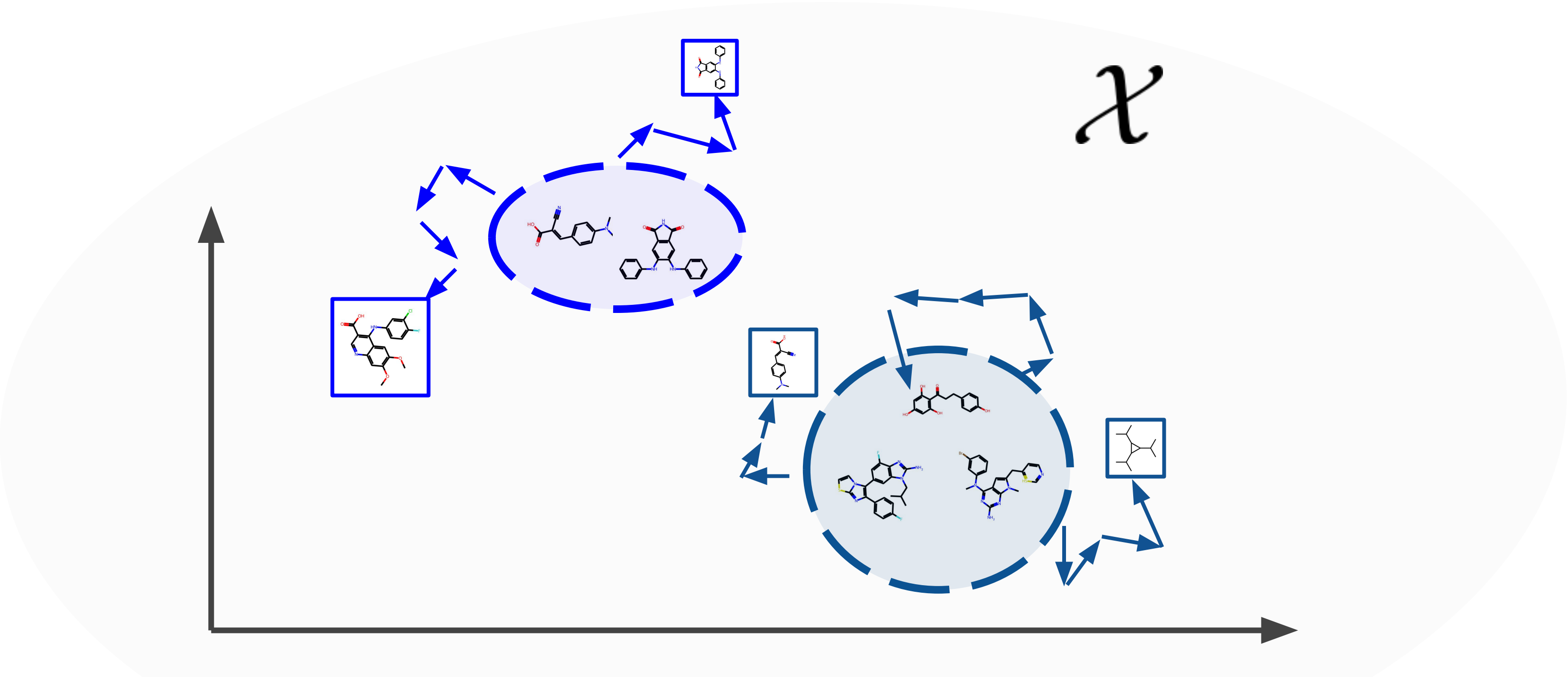


Figure from: Strandgaard, M., Seumer, J., Benediktsson, B., Bhowmik, A., Vegge, T., & Jensen, J. H. (2023). Genetic algorithm-based re-optimization of the Schrock catalyst for dinitrogen fixation. *PeerJ physical chemistry*, *5*, e30.

Genetic Algorithms for molecular generation

In our molecular space, GAs perform local search around existing clusters.



Part 1: Setting up and exploring `medchem` and `graph-ga`

- **MedChem**

  Offers several filtering options for medicinal chemistry

  For more info, go to: medchem-docs.datamol.io/stable/

- **Graph GA**

  Offers several filtering options for medicinal chemistry

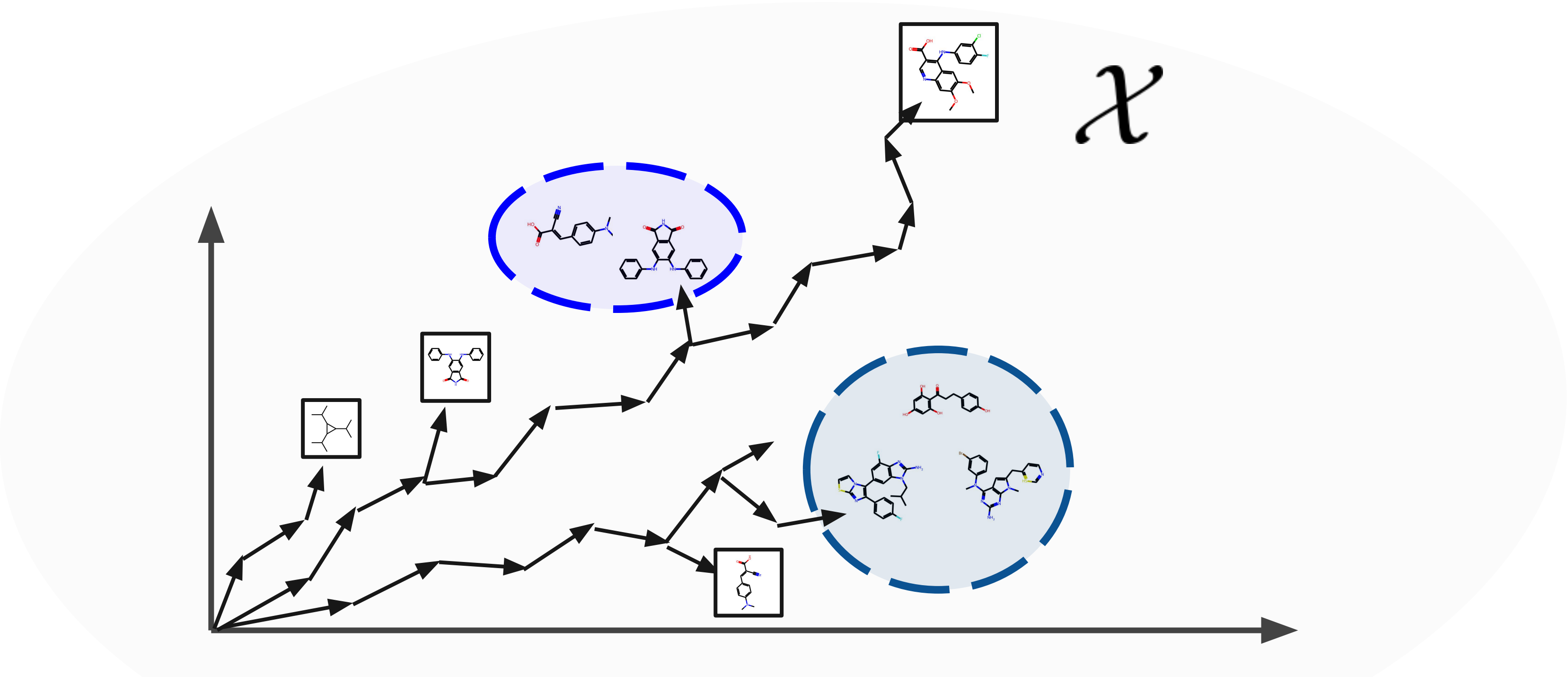
  For more info, go to: github.com/AustinT/mol_ga

Go through Part 1 in the Colab Notebook

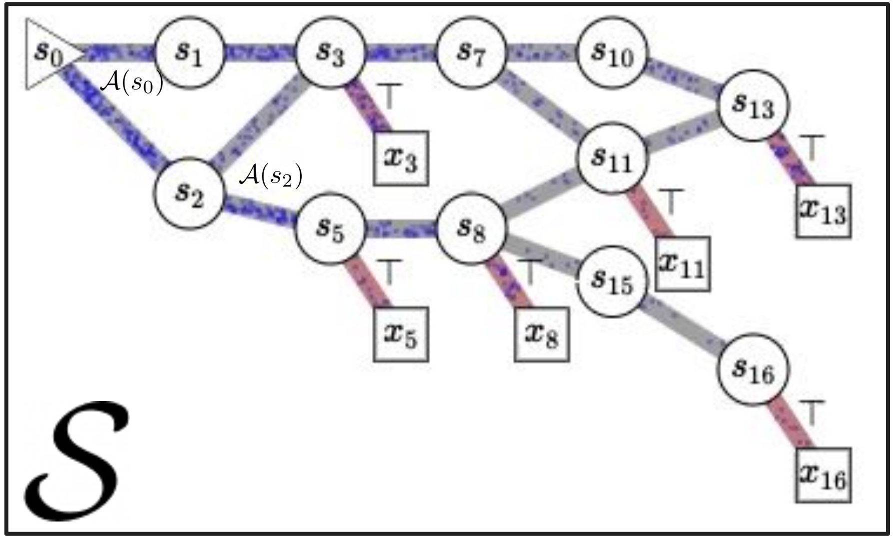
Ends at 15:30 !

Molecular Generation as Sequential Decision Making

In our molecular space, GFlowNets create new molecules by starting from the origin (empty set)



GFlowNets basics



A GFlowNet learns a flow of probability from state to state to sample objects proportionally to their reward:

$$p_\pi(x) = \frac{r(x)}{Z} \quad , \quad Z := \sum_{x' \in \mathcal{X}} x'$$

Fragment GFN

In a fragment GFN for molecular generation, states are molecules and actions are fragments

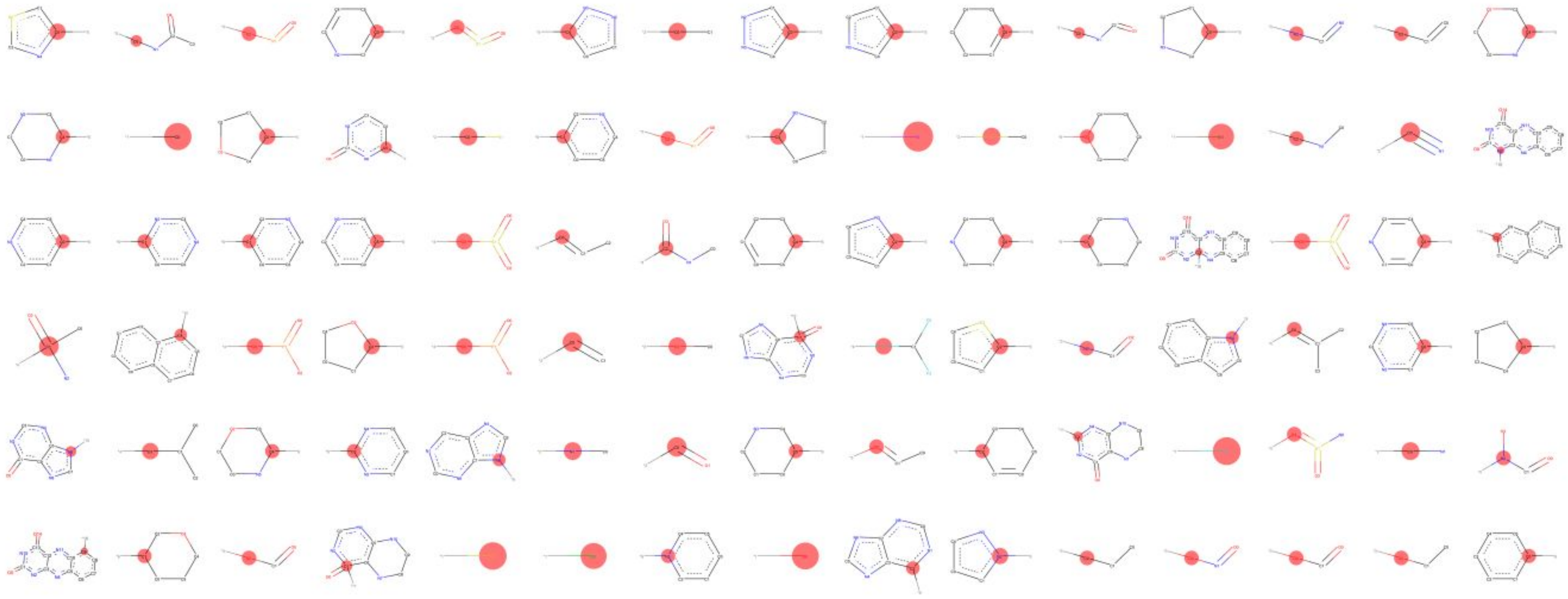
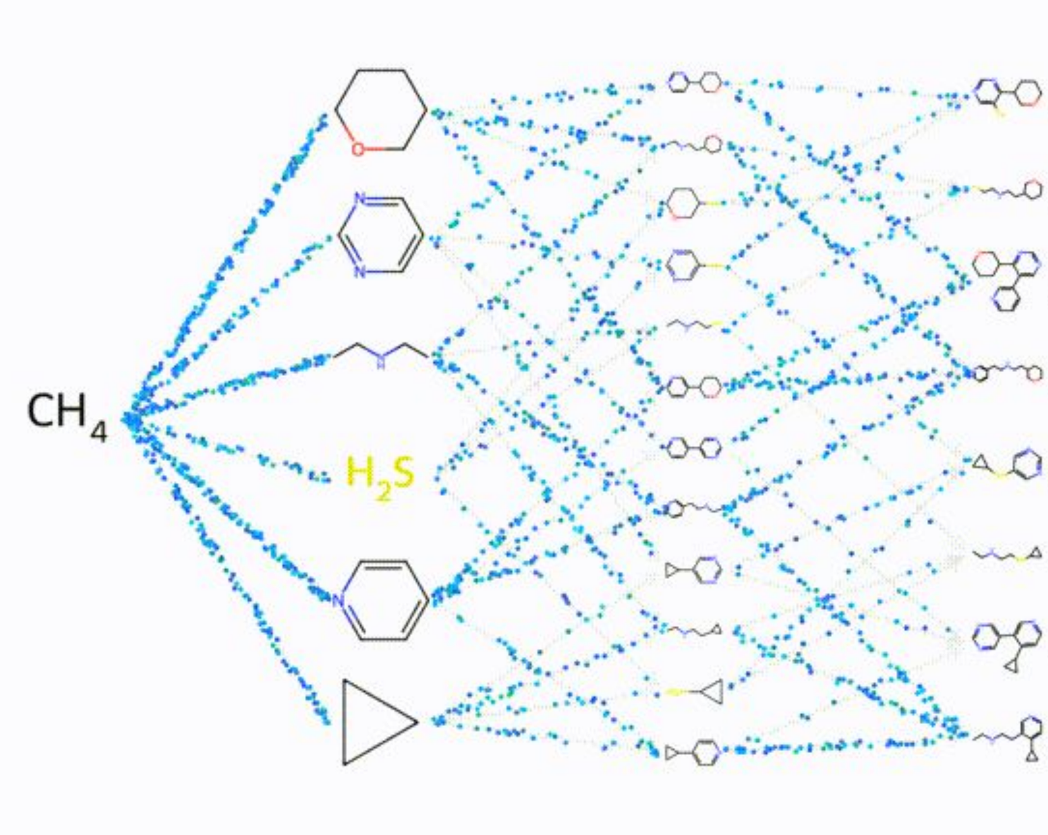


Figure from: Bengio, E., Jain, M., Korablyov, M., Precup, D., & Bengio, Y. (2021). Flow network based generative models for non-iterative diverse candidate generation. *Advances in Neural Information Processing Systems*, *34*, 27381-27394.

Fragment GFN

Given enough time to learn and explore, our GFN will learn to sample terminal states (finished molecules) according to their score.



Part 2: Exploring `gflownet` for fragment-based design

- **Gflownet codebase**

  Specialised for compositional object generation on graphs
  In our case, we are building graphs of molecular fragments!

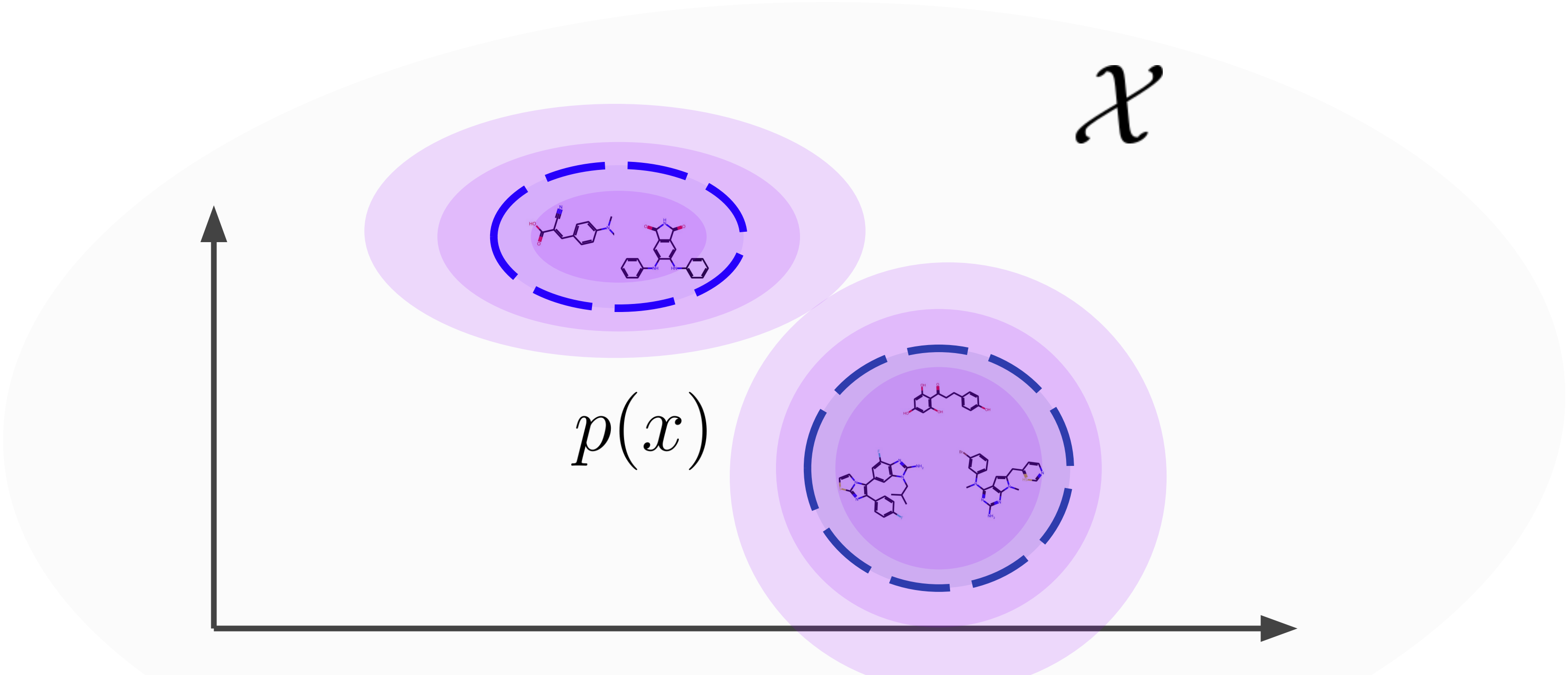
  For more info, go to: github.com/recursionpharma/gflownet

Go through Part 2 in the Colab Notebook

Ends at 16:45 !

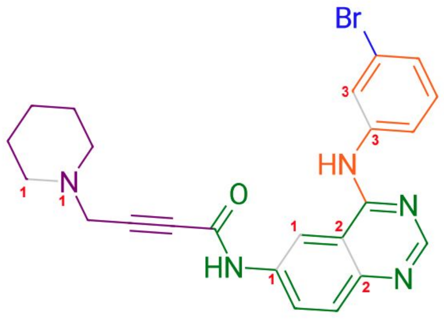
Molecular Generation from Likelihood Models

In our molecular space, language models learn a probability distribution around the known molecular clusters.



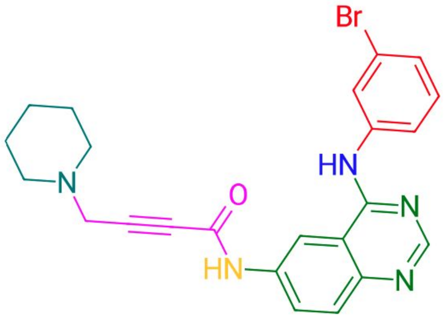
SAFE encoding

SMILES



O=C(C#CCN1CCCCC1)Nc1ccc2ncnc(Nc3cccc(Br)c3)c2c1

SAFE

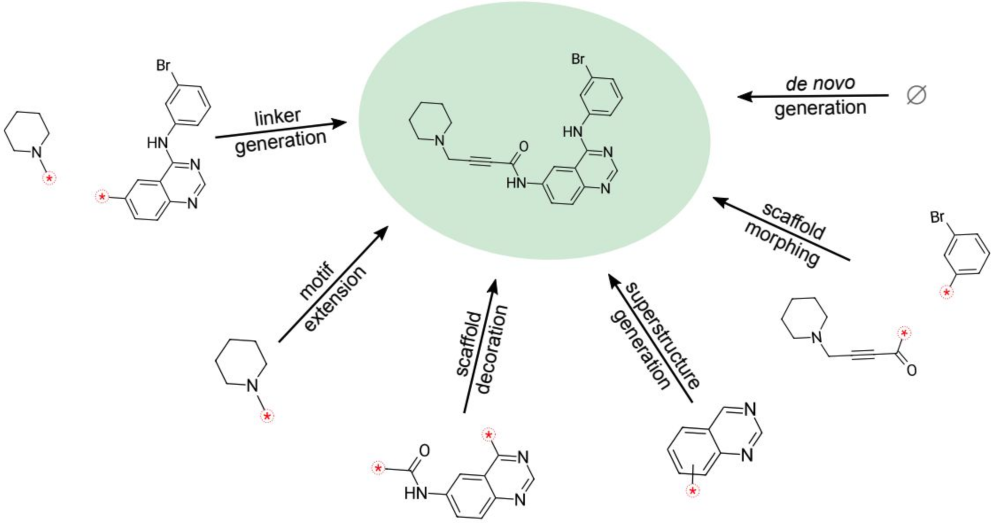


N18CCCCC1.O=C6C#CC8.N67.c17ccc2ncnc4c2c1.N45.c15cccc(Br)c1

SAFE Scaffold Decoration

Dataset

```
C12C3C14.CC2C.C3(C)C.C4(C)C
c14cc2ncc8c6c2cc15.c17ccc(F)c(Cl)c1.C8(=O)O.CO4.N67.O5C
O=C1NC(=O)c2cc4c6cc21.c15ccccc1.c17ccccc1.N45.N67
c12ccc(C=3)cc1.C=3(C#N)C(=O)O.CN2C
c13nc(N)nc2c1cc5n2C.c14cccc(Br)c1.C5C1=[SH]C=NC=C1.CN34
O=C1NC(=O)c2cc4c6cc21.c15ccccc1.c17ccccc1.N45.N67
c12c(O)cc(O)cc1O.c13ccc(O)cc1.O=C2CC3
n15c(N)nc2c(F)cc6cc21.c16c7nc2sccn12.c17ccc(F)cc1.CC(C)C5
```



Transformer

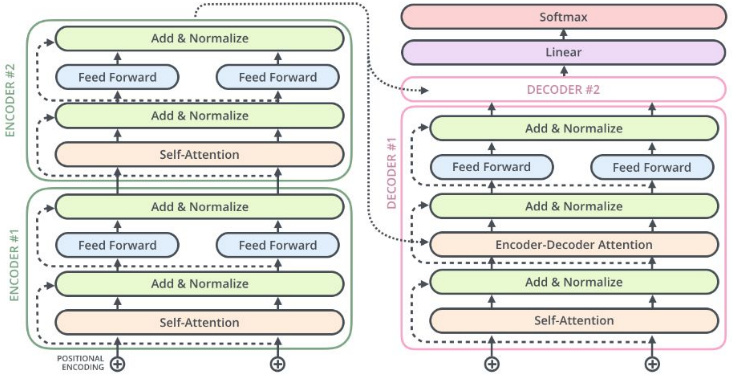


Figure from: jalammar.github.io/illustrated-transformer/

Part 3: Exploring `safe` for language-based design

- **SAFE**

  SAFEs are a newly proposed molecular string representation which allows for a variety of tasks from a single language model.

  In this lab, we use SAFE-GPT to refine a candidate molecules with scaffold decoration.

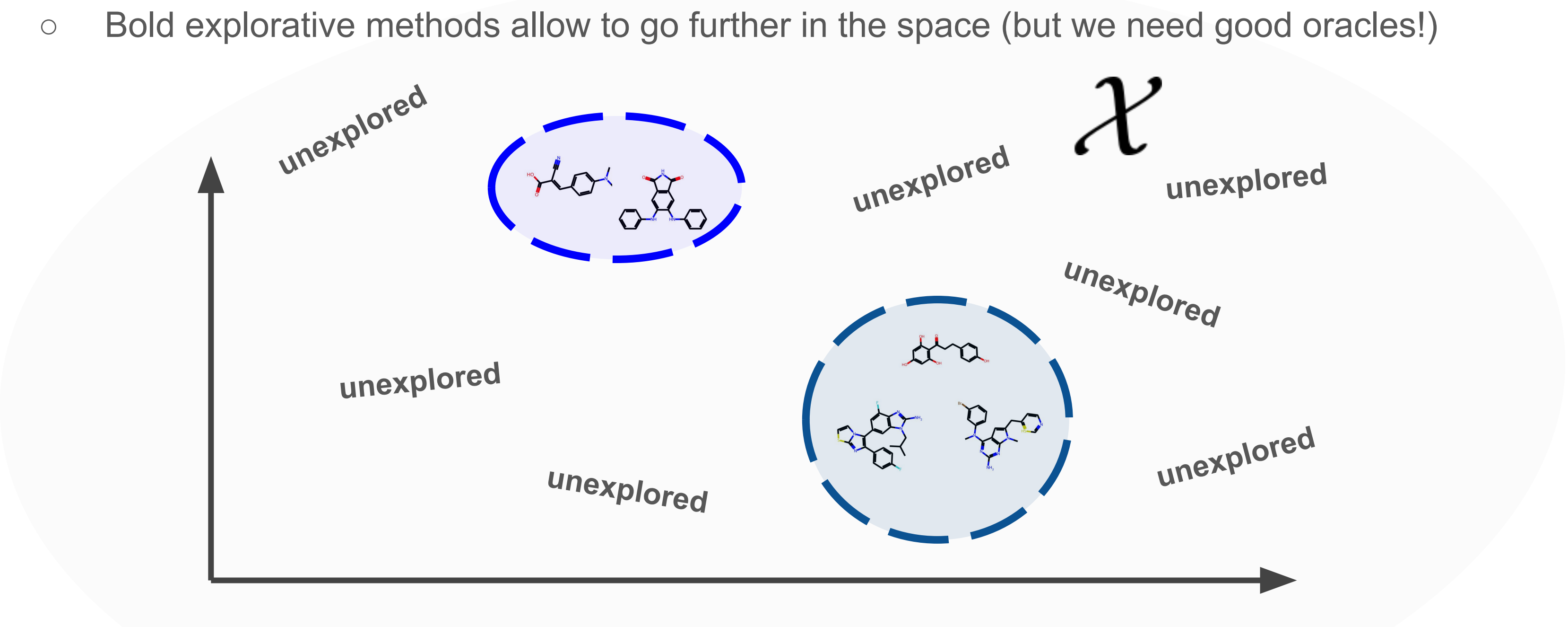
  For more info, go to: github.com/datamol-io/safe

Go through Part 3 in the Colab Notebook

Ends at 17:15 !

Recap: different approaches to molecular generation

- **The Molecular Space is vast, and we need different approaches for different tasks**
  - Fine-grained methods and local search are crucial for lead optimization
  - Likelihood-based methods represent inductive biases towards what we know works
  - Bold explorative methods allow to go further in the space (but we need good oracles!)



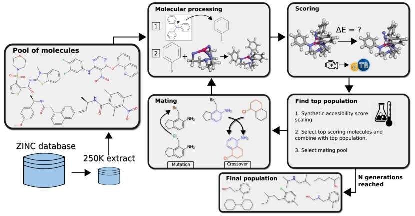
Recap: different approaches to molecular generation

- ## Genetic Algorithms

  Local search based on fitness function.

  Genetic algorithms are strong baselines for molecule generation

  A graph-based genetic algorithm [...] for the exploration of chemical space



- ## Generative Flow Networks (GFlowNets)

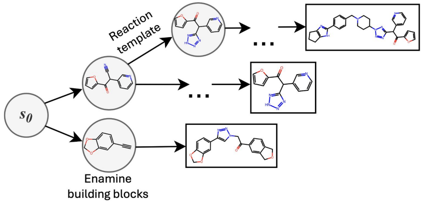
  Molecular generation as a sequential decision making process.

  Learns to samples new molecules proportionally to their score.

  Flow Network based Generative Models for Non-Iterative Diverse Candidate Generation

  Goal-conditioned GFlowNets for Controllable Multi-Objective Molecular Design

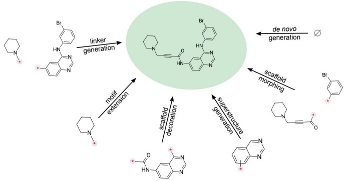
  SynFlowNet: Towards Molecule Design with Guaranteed Synthesis Pathways



- ## SAFE GPT

  Language-based molecular generation applying to a variety of generative tasks.

  Gotta be SAFE: A New Framework for Molecular Design



Summer School Lab

The End.

Connect with us

Any questions, ideas or other feedback?
We would love to hear from you!

Presented by

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