LING682 FINAL PROJECT

Controlled Molecular Generation

Using Sequential Monte Carlo Sampling with Small Language Models

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The Challenge

De Novo Discovery

Modern drug discovery aims to reveal novel, valid compounds satisfying specific physicochemical properties. Traditional methods are limited by predefined rules and fragment libraries that restrict accessible chemical space.

The Control Problem

A persistent challenge in AI-based generation is achieving reliable control over properties like **Molecular Weight (MW)**, **Lipophilicity (logP)**..etc without incurring massive computational costs.

Sequential Monte Carlo (SMC)

1. Importance Sampling

Estimates expectations under an intractable target distribution by drawing samples from a proposal distribution and reweighting them effectively.

2. Sequential Update

Weights are updated dynamically as tokens are appended. Potential functions score how well a partial sequence matches the desired constraints.

3. Adaptive Resampling

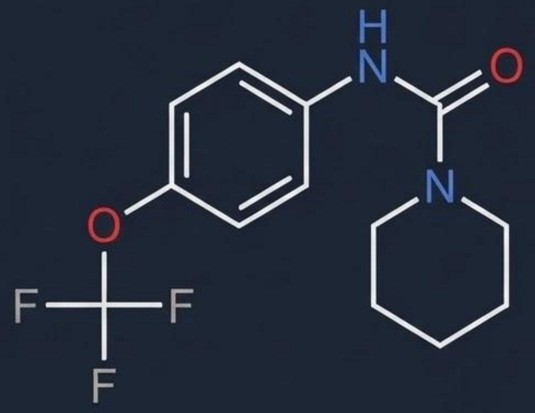
Prevents particle collapse by replicating high-weight particles and discarding low-weight ones.

Experimental Setup

We compare a small model against a massive fine-tuned model on constrained molecules generation.

Feature	GPT2-ZINC	Smiley Llama
Size	87 Million	8 Billion
Training	ZINC (~480M)	ChEMBL (~2M)
Input	SMILES Prefix	Natural Language
Method	SMC-Guided	Fine-tuning

Chemical Structure Input



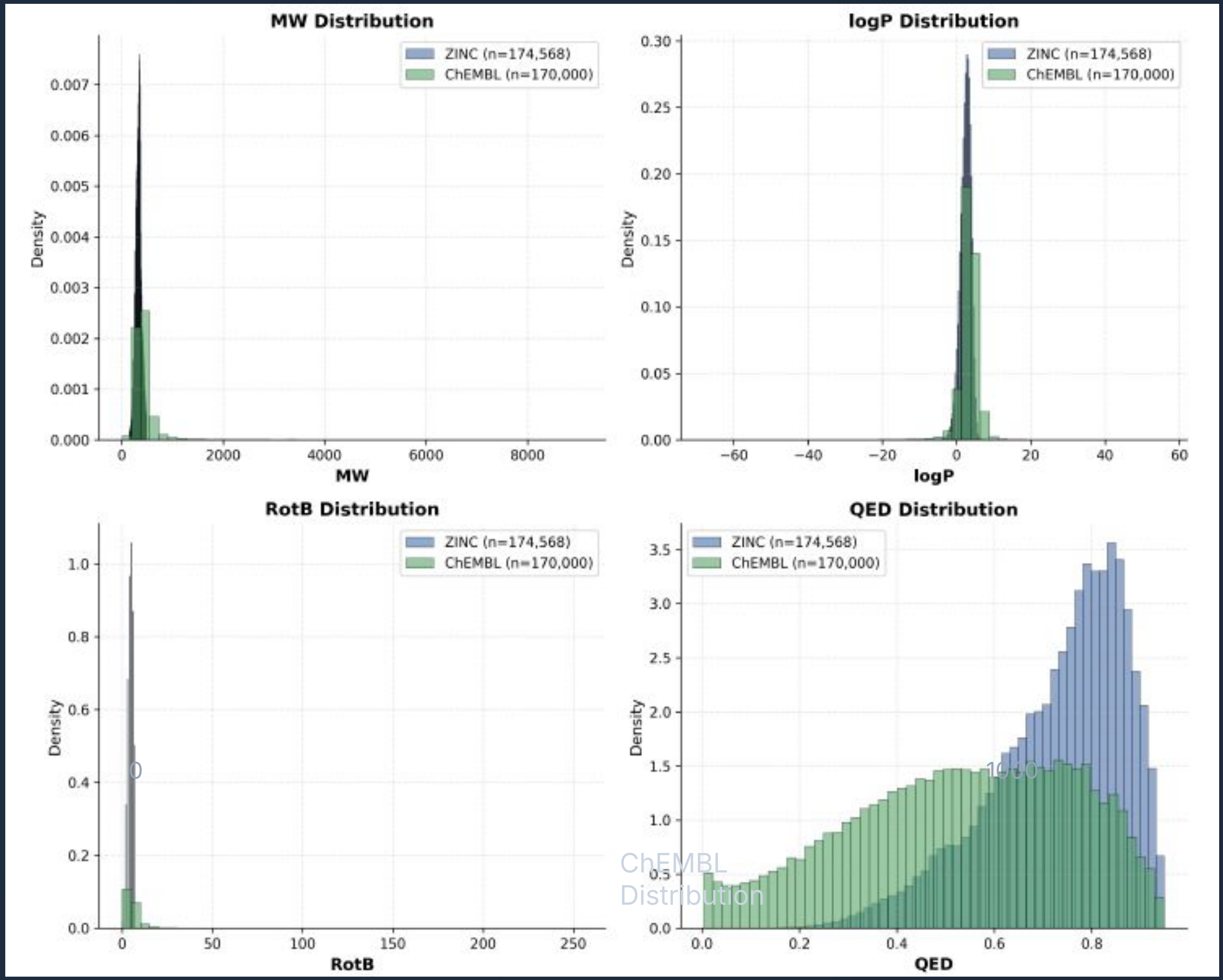
SMILES String:
O=C(Nc1ccc(OC(F)(F)F)cc1)N1CCCCC1

Data Distribution Analysis

Property Overlap

Despite the immense difference in dataset size (ZINC: ~480M vs ChEMBL: ~2M), the distributions of key properties are remarkably similar.

- ✓ **ZINC :** High density in drug-like space.
- ✓ **ChEMBL :** Broad pharmacological coverage.
- ✓ **Conclusion:** The chosen properties (MW, logP, RotB) follow similar manifolds in both datasets, ensuring a fair comparison of generative capabilities.



Constraint Paradigms

Range-Based

Testing strict dual-bound control derived from data percentiles.

- ✓ **Loose:** 5th-95th percentile
- ✓ **Tight:** 25th-75th percentile
- ✓ **Ultra-tight:** 40th-60th percentile

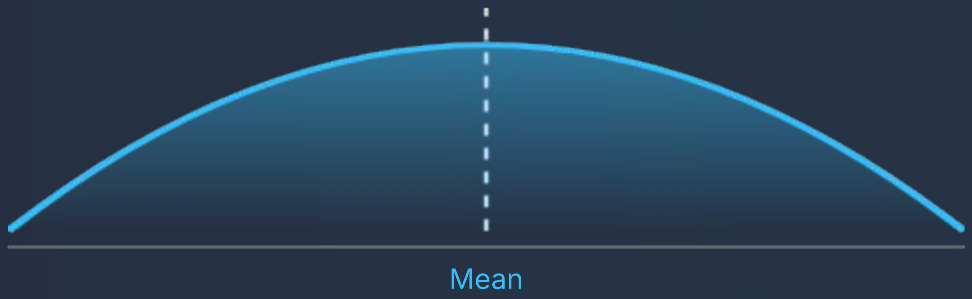
Gradual (Upper-Bound)

Matching instruction-following formats with increasing difficulty.

- ✓ **Loosen:** MW ≤ 500
- ✓ **Tight:** MW ≤ 400, logP ≤ 4
- ✓ **Ultra-tight:** MW ≤ 350, logP ≤ 3.5, RotB ≤ 8

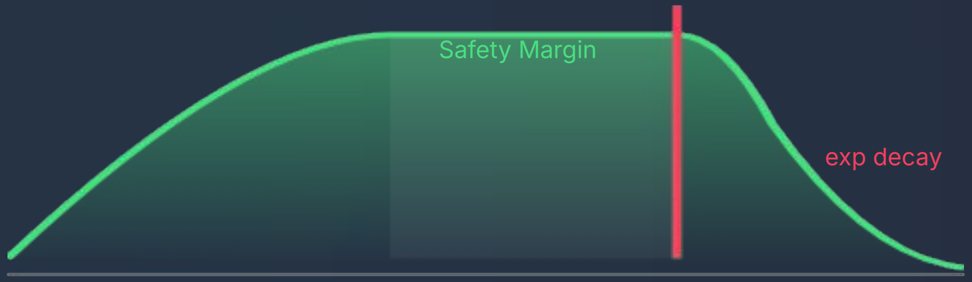
Reward Design

We shift from binary filtering to continuous optimization, shaping the reward surface to guide particles toward valid regions.



Symmetric (Range)

Centers the optimizer in the middle of the range for maximum robustness.



Asymmetric (Bound)

Penalizes violations while rewarding a "Safety Margin" buffer zone.

Initialization Prefixes

To prevent mode collapse and ensure structural diversity, we initialize SMC particles with 20 distinct chemical prefixes ranging from aromatic rings to aliphatic chains.

C1=CC=	Aromatic Core
CCN	Amino Aliphatic
COC	Polar Ether
CC(=O)	Carbonyl
C1CN	Heterocycle
CCS	Sulfur Motif
CCOCON	Extended Polar
CCC	Generic Aliphatic
C1CCCCC1	Aliphatic Ring
c1ccccc1	Benzene
n1ccccc1	Pyridine
N1CCCCC1	Piperidine
O1CCNCC1	Morpholine
NC(=O)	Amide
NS(=O)(=O)	Sulfonamide
NC(=O)N	Urea
C#N	Nitrile
Clc1ccccc1	Aryl Chloride
P(=O)(O)O	Phosphonate
COC	Ether Builder

Results

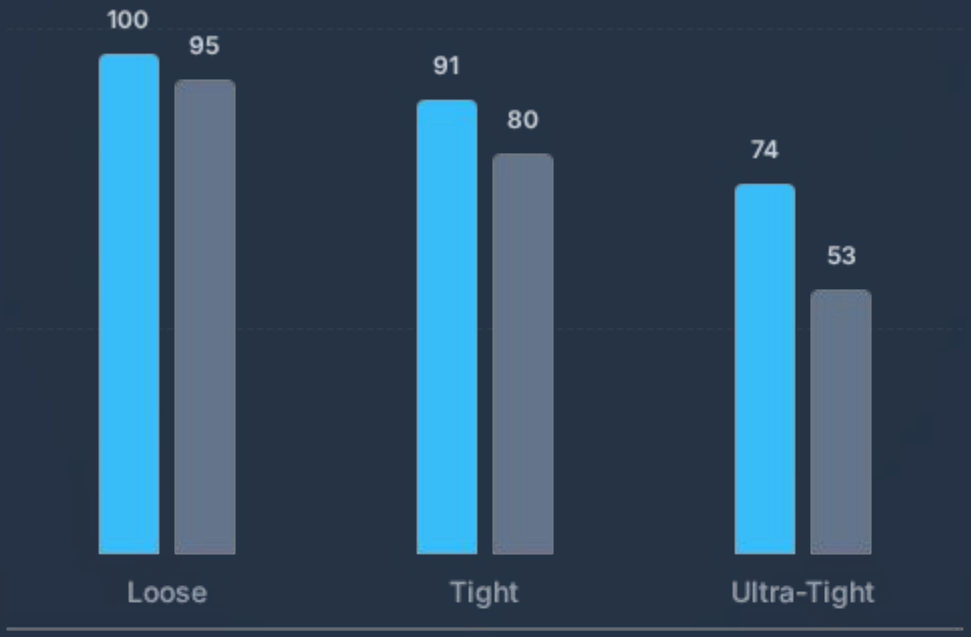
100%

Validity

Perfect structural validity achieved across all models and constraint settings.

Adherence %

Comparison under "Gradual" constraints.



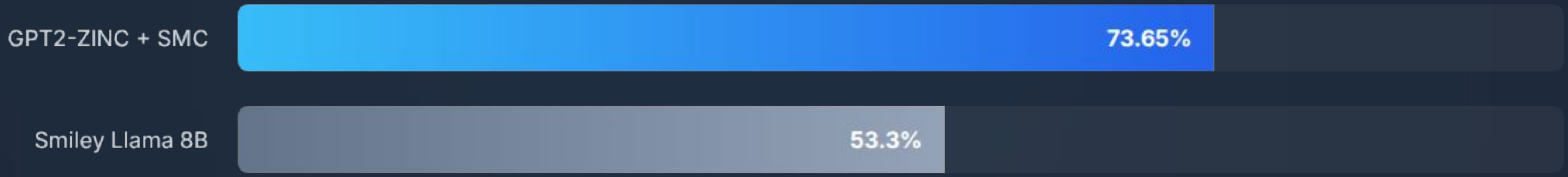
0.91

Diversity

High chemical diversity maintained via distinct prefix initialization.

Highlight: Ultra-Tight Constraints

Comparing the percentage of generated molecules that strictly adhere to the most difficult "Gradual" constraints.



💡 **Insight:** Despite being ~100x smaller, the SMC-guided model outperforms the 8B parameter model by over 20 percentage points.

Key Takeaways

Small Models Could Win

A specialized small model (87M) with SMC can rival or surpass a larger fine-tuned model (8B).

SMC Effectiveness

Potential-based rewards steer generation towards desired properties without fine-tuning.

Computational Efficiency (Not 100% confirmed)

This approach operates at a fraction of the cost of large-scale inference.

Current Limitations

Extremely narrow, dual-bound ranges remain a difficult open problem.

Future Work

Non-Linear Restrictions

Refining SMC potentials to handle more complex chemical constraints beyond simple ranges.

Multi-Property Balancing

Developing sophisticated weighting mechanisms to balance conflicting objectives.

Core-Driven Synthesis

Exploring scaffold-based generation where the model builds around a fixed core.