The narrative report should provide an overall description of your conference presentation experience, be 2-3 pages in length, double-spaced, and should contain the following components:

* An overview of your research project and your conference presentation experience (including any challenges, surprises, changes you would make for your next presentation, etc.);
* Reflection on the experience of presenting your research in either a virtual environment or in-person;
* Reflection on how this experience will impact your time left at Harvard and advance your thesis and/or interest in the topic; and
* A description of the interaction with your faculty sponsor (if any).

Dear URAF Conference Funding Committee,

I am writing to thank you for the support that allowed me to present our project, "Multi-objective generative AI for designing novel brain-targeting small molecules", at the 2024 Generative and Experimental Perspectives for Biomolecular Design (GEM) workshop, part of the 12th International Conference on Learning Representations (ICLR), that took place from May 7th to May 11th, 2024, in the city of Vienna, Austria. This work was conducted under the guidance of Prof. Nada Amin, Assistant Professor of Computer Science at Harvard University, as part of COMPSCI 252R: Advanced Topics in Programming Languages and COMPSCI 91R: Supervised Reading and Research during the Fall 2023 and Spring 2024 semesters.

In our study, we focus on identifying small molecule drug candidates for central nervous system (CNS) diseases that currently lack effective treatments. The blood-brain barrier (BBB) poses a significant challenge in delivering drugs to the CNS, hindering both diagnosis and treatment. Computational methods that generate BBB-permeable lead compounds *in silico* could be valuable tools in the CNS drug design process. However, in practical applications, BBB penetration alone is not sufficient; molecules must also perform a desired function, such as binding to a specific target or receptor in the brain, while being safe and non-toxic for human use.

To address these challenges, we employed multi-objective generative AI to synthesize drug-like, BBB-permeable small molecules with high predicted binding affinity to a disease-relevant CNS target. We specifically focused on designing molecules with predicted bioactivity against dopamine receptor D2, which is the primary target for most clinically effective antipsychotic drugs. After training several graph neural network-based property predictors, we adapted SyntheMol (Swanson et al., 2024), a recently developed Monte Carlo Tree Search-based algorithm originally designed for antibiotic discovery, to perform a multi-objective guided traversal over an easily synthesizable molecular space.

As a result, we designed a library of 26,581 novel and diverse small molecules containing hits with high predicted BBB permeability, favorable predicted safety and toxicity profiles, and the potential for straightforward synthesis and experimental validation in the wet lab. We also validated top-scoring molecules using molecular docking simulation against the D2 receptor, demonstrating predicted binding affinity comparable to risperidone, a clinically prescribed D2-targeting antipsychotic. We hope that our SyntheMol-based computational approach will enable the discovery of novel neurotherapeutics for currently intractable CNS disorders in the future.

I completed this project together with fellow undergraduate and co-first author Ayush Noori. Ayush and I divided the work for this project equally: we designed the algorithmic paradigm together, Ayush curated the labeled data to train molecular property predictors, I developed the training loop and adapted the Monte Carlo Tree Search algorithm, Ayush performed the molecular simulations, and we drafted the paper together. We also jointly designed the poster and presented it together at ICLR GEM 2024.

I am deeply thankful for the support of the Office of Undergraduate Research and Fellowships, which enabled both of us to attend one of the premier deep learning conventions and present our work to the global scientific community. Attending ICLR 2024, my first research conference, was truly a transformative experience. It broadened my understanding of the research world and gave me a new perspective on the jobs that scientists take after moving on from academia. Ayush and I showcased our research during two GEM poster sessions and received overwhelmingly positive feedback from attendees, including experts in computer science and biomolecular design. Many visitors expressed excitement about the synthesizability guarantee that the algorithm provided for generated molecules, and framed it as a great feature within the context of the workshop talks, where it was made clear that synthesizability was a great problem with the molecules generated by the state of the art diffusion models.

Discussions regarding how we could improve or extend our paper were extremely valuable. I learned how we could have made our binding affinity benchmark more accurate, and what other binding targets were currently of high priority in the research world. As I dig deeper into the world of computational biology and the intersection of machine learning and health, some of interactions with authors and papers from the posters I saw will be extremely useful:

* “Removing Biases from Molecular Representations via Information Maximization” by Wang *et al.* This new representation method showed superior performance in molecular property prediction and could prove very useful for extending our paper.
* “CoRe-GD: A Hierarchical Framework for Scalable Graph Visualization with GNNs” by Grötschla *et al.* This new method will be useful for displaying the vast biological knowledge graph powering drug repurposing predictions in Ayush’s and my new collaboration project: GRAVITY.
* “Less is More: One-shot Subgraph Reasoning on Large-scale Knowledge Graphs” by Zhou *et al.* could also be useful for GRAVITY, as it could enable a higher degree of explainability for predictions made from a knowledge graph.

Outside of the GEM workshop, the corporate booths at the conference allowed me to interact with researchers from companies at the forefront of the machine learning field, such as Google Research and DeepMind, as well as discover the Chinese counterparts to many of these American companies leading AI research, such as Zhipu AI, Unitree, and Meituan. By speaking to their researchers I was able to understand their vision for the future and how they fit in the global landscape. Conversations with DeepMind software engineers also led me to discover the role of Research Engineers, which I believe fits my profile better than the researcher role, and for which I plan on applying for next year.

The Generative Artificial Intelligence side-event was a great opportunity to meet like minded individuals interested in applying the latest research to entrepreneurial pursuits. One of the people that struck out the most was Dr. Martin Szummer, founder and CTO of VocalIQ, a spoken dialog company that made a self-learning voice interface and that was bought by Apple as part of the Siri project. With him, and with Walden Yan, Harvard alumnus and co-founder of Cognition AI, we talked about the culture of Generative AI applied to the code writing and maintenance within large, mostly corporate, codebases. These conversations were incredibly insightful and tied in perfectly with my future thesis research into code generating agents.

Other papers in the larger conference covered LLM programming agents and caught my eye. “Executable CodeACtions Elicit Better LLM Agents” by Wang *et al.* introduced a new action space (CodeAct) for large language models to process information they receive and act on it. This method, which provides agents with a Python environment that allows them to execute arbitrary queries, was shown to improve the effectiveness and efficiency of language models. “Tailoring Self-Rationalizers with Multi-Reward Distillation” by Ramnath *et al.* showed that LMs orders of magnitude smaller than GPT-3, a common model for code generation, could outperform it for a restricted set of tasks if configured correctly. This opens the gates for the use of small but powerful single-purpose models that could greatly reduce the cost of operating a code-generating network of agents.

Also through the code generation workshop at the conference, I had the opportunity to meet and spend the afternoon and evening with Parth Sarthi, Salman Abdullah, Aditi Tuli, Shubh Khanna, Anna Goldie, the authors of “RAPTOR: Recursive Abstractive Processing for Tree-Organized Retrieval”. They are undergraduate students at Stanford and researchers at Dr. Christopher Manning’s lab. I was able to learn from their experience also turning a class project into a conference paper and from their views on the future of Retrieval-Augmented Generations. Not only was it a great learning experience but it also left me with friendships that can flourish in the future whenever I visit Stanford.

That same evening I got the opportunity to spend time with Harvard alumnus Luke Melas-Kyriazi, who is a Rhodes Scholar and PhD student at Oxford University. He talked about how much he enjoyed his undergraduate experience on campus and gave his thoughts on how to craft a successful and fulfilling trajectory after graduation.

Overall the conference and the week in Vienna were incredible opportunities to receive feedback on our research, learn more about the industry, and interact with like-minded individuals. Once again, I extend my sincere gratitude for the funding provided to attend the GEM workshop at ICLR 2024, which turned out to be an exceptional and unparalleled opportunity for learning and professional development.

Sincerely,

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Ayush Noori and me, right after the final round of poster presentations.