GFLOWNETS FOR LEARNING BETTER DRUG-DRUG INTERACTION REPRESENTATIONS

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1 INTRODUCTION

Drug–drug interactions (DDIs) represent a critical issue in clinical pharmacology, as adverse interactions can lead to significant patient harm and reduced therapeutic efficacy (Zhao et al., 2023). Numerous computational models have been developed to predict DDIs, leveraging diverse features from chemical structures to biological networks (Dai et al., 2020; Yang et al., 2022). However, a pervasive challenge in this domain is the severe class imbalance among interaction types. Common interaction types, such as synergistic effects or well-characterized adverse reactions, dominate the datasets, while rare interaction types remain under-represented (Ezzat et al., 2016). This imbalance hinders the model's ability to learn nuanced patterns associated with infrequent interactions. As a consequence, predictive performance on rare, yet clinically significant, interaction types suffers. The disparity in data distribution thus poses an urgent need for innovative solutions in DDI prediction.

In light of the class imbalance, existing state-of-the-art methods are often trained in a binary setting (Dai et al., 2020; Wasi et al., 2024; Ngo et al., 2022), treating the DDI prediction task as a simple presence-or-absence problem. This binary framing tends to disregard the inherent heterogeneity among different interaction types. Consequently, the models become biased towards common interaction types and fail to adequately capture the underlying characteristics of rare classes. The motivation for this work stems from the recognition that a one-size-fits-all approach is insufficient for capturing the diversity of DDIs. Addressing the imbalance is crucial for improving the reliability and clinical utility of these predictions (Dai et al., 2020). By acknowledging and explicitly targeting the disparity in interaction frequencies, we aim to bridge the gap between theoretical performance and real-world application with GFlowNets (Nica et al., 2022; Roy et al., 2023).

To mitigate the challenges posed by class imbalance, we propose an innovative framework that integrates a Generative Flow Network (GFlowNet) (Bengio et al., 2023; Jain et al., 2023) module with a Variational Graph Autoencoder (VGAE) (Ngo et al., 2022; Wasi et al., 2024; **?**). Our approach first computes a reward for each interaction type that is inversely proportional to its frequency, thereby guiding the sampling process towards under-represented classes. The GFlowNet module sequentially generates synthetic DDI samples by first selecting an interaction type based on this reward and then sampling a drug pair conditioned on that type. These synthetic samples are then used to augment the original training data, effectively balancing the class distribution. Experimental results indicate that this method enhances the model's ability to predict both common and rare interaction types with improved robustness. The proposed framework not only addresses a critical limitation in current DDI prediction models but also holds promise for broader applications in imbalanced classification problems across biomedical domains.

2 MODEL ARCHITECTURE

In this work, we address the class imbalance in DDI prediction by integrating a GFlowNet module into a VGAE framework, following Ngo et al. (2022). In brief, the VAE learns latent drug embeddings for downstream interaction prediction, while the GFlowNet module generates synthetic DDI samples for rare interaction types by sampling with probabilities proportional to a reward function.

Variational Autoencoder for DDI Prediction. Let the training set be $\mathcal{D}_{\text{train}} = \{(d_i, d_j, t) \mid d_i, d_j \in \mathcal{D},\ t \in \mathcal{T}\}$, where $\mathcal{D}$ is the set of drugs and $\mathcal{T}$ the set of interaction types. Each drug $d \in \mathcal{D}$ is encoded into an embedding $\mathbf{e}_d \in \mathbb{R}^D$ via an encoder $q_\phi(\mathbf{z} \mid d)$, and a decoder $p_\theta(d_i, d_j \mid t, \mathbf{z}_i, \mathbf{z}_j)$ reconstructs the interaction conditioned on the latent codes. The VGAE is trained by minimizing the objective,

$$\mathcal{L}_{\text{VAE}}(\theta, \phi) = -\mathbb{E}_{q_\phi(\mathbf{z}|d_i,d_j,t)}\left[\log p_\theta(d_i, d_j \mid t, \mathbf{z}_i, \mathbf{z}_j)\right] + \text{KL}\left(q_\phi(\mathbf{z} \mid d_i, d_j, t) \,\|\, p(\mathbf{z})\right), \quad (1)$$

Table 1: Experimental Findings

Setup	AUROC	Accuracy	AUPRC	F1 Score	SE	JSV	Coverage
Without GFN	0.99081	0.96859	0.98861	0.98982	1.23	0.35	0.2441
With GFN	0.99071	0.96792	0.98922	0.99914	1.69	0.12	0.7709

where $p(\mathbf{z})$ is the prior distribution over the latent space.

GFlowNet Module for Synthetic Sample Generation. To improve prediction on under-represented interaction types, we augment the training data with synthetic samples generated via GFlowNet. This module is responsible for sequentially constructing a DDI sample in two steps: (i) sampling an interaction type and (ii) sampling a pair of drugs conditioned on the selected type.

For each interaction type $t \in \mathcal{T}$, let $n_t = \sum_{(d_i,d_j,t') \in \mathcal{D}_{\text{train}}} \mathbb{I}\{t' = t\}$ denote its frequency in the training set. We then define a reward $r(t) = \frac{1}{n_t + \epsilon}, \quad \epsilon > 0$, and normalize these rewards to obtain a probability distribution $p(t) = \frac{r(t)}{\sum_{t' \in \mathcal{T}} r(t')}$. A type is sampled by drawing, $t \sim p(t)$. Given the sampled type t, a candidate set $\mathcal{C} \subset \mathcal{D} \times \mathcal{D}$ is constructed. For each candidate pair $(d_i, d_j) \in \mathcal{C}$, a score is computed as $s_{ij}^{(t)} = \sigma\Big(f_\theta(\mathbf{e}_i, \mathbf{e}_j; t)\Big)$, where $\sigma(\cdot)$ is the sigmoid function and $f_\theta(\cdot)$ represents the decoder network's output conditioned on t. The candidate pair with the highest score is selected: $(d_i^\star, d_j^\star) = \arg\max_{(d_i,d_j) \in \mathcal{C}} \; s_{ij}^{(t)}$. The synthetic sample is then given by $\tilde{x} = (d_i^\star, d_j^\star, t)$.

Training with Augmented Data. A set $\mathcal{D}_{\text{synth}}$ of N synthetic samples is generated using the procedure described above. The augmented training set is defined as $\mathcal{D}_{\text{aug}} = \mathcal{D}_{\text{train}} \cup \mathcal{D}_{\text{synth}}$. The VAE is retrained on $\mathcal{D}_{\text{aug}}$ by minimizing the loss in Eq. equation 1.

3 Experiments, Results and Discussion

In this preliminary work, we use the DrugBank dataset (Wishart et al., 2018), which includes 1,703 drugs and 191,870 drug pairs spanning 86 DDI types, along with structural and chemical information. The dataset was split into three subsets: 115,185 drug pairs for training, 38,348 for validation, and 38,337 for testing. We implemented VGAE for DDI prediction as per Ngo et al. (2022), given its generative nature. The results in Table 1 show the impact of adding the GFlowNet module to the VGAE framework for DDI prediction. AUROC, Accuracy, AUPRC, and F1 scores were all above 0.99, with minor differences in classification metrics, suggesting GFlowNet had little impact on performance. However, diversity and coverage metrics showed substantial improvements, demonstrating GFlowNet's effectiveness in addressing class imbalance.

Shannon Entropy (SE) (Fang & Tsao, 2008) increased from 1.23 to 1.69, indicating better balance in interaction types. Jensen–Shannon Divergence (JSD) (Menéndez et al., 1997) decreased from 0.35 to 0.12, reflecting closer alignment with the true interaction distribution. Coverage improved from 0.2441 to 0.7709, indicating better learning of rare interaction types, which enhances real-world applicability. While standard classification metrics showed minimal changes, the diversity metrics reveal significant improvements. This suggests that generative methods in DDI prediction can address class imbalance, especially for rare interactions, which are crucial for clinical settings.

4 Conclusion

This work introduces a novel approach to tackling class imbalance in drug–drug interaction prediction by integrating a GFlowNet-based generative sampling strategy into a VGAE framework. While traditional classification metrics remain largely unchanged, diversity-aware evaluations show significant improvements, highlighting GFlowNet's ability to discover under-represented interaction types, crucial for patient safety in clinical applications. Future work will focus on extending the framework to larger, more diverse datasets and optimizing sampling strategies to improve rare class representation.

MEANINGFULNESS STATEMENT

In computational biology, models must reflect the complexity of biological interactions and perform equitably across common and rare phenomena. Our work addresses class imbalance in drug–drug interaction (DDI) prediction by integrating a GFlowNet-based generative sampling strategy into a VGAE framework. This improves the model's ability to identify rare, clinically significant interactions, enhancing both predictive accuracy and fairness. By boosting diversity in generated samples, our approach contributes to more reliable, interpretable, and clinically actionable AI models, emphasizing the importance of addressing class imbalance for better healthcare outcomes.

URM STATEMENT

The authors acknowledge that at least one key author of this work meets the URM criteria of ICLR 2025 Tiny Papers.

REFERENCES

Yoshua Bengio, Salem Lahlou, Tristan Deleu, Edward J. Hu, Mo Tiwari, and Emmanuel Bengio. Gflownet foundations. *Journal of Machine Learning Research*, 24(210):1–55, 2023. URL http://jmlr.org/papers/v24/22-0364.html.

Yuanfei Dai, Chenhao Guo, Wenzhong Guo, and Carsten Eickhoff. Drug–drug interaction prediction with Wasserstein Adversarial Autoencoder-based knowledge graph embeddings. *Briefings in Bioinformatics*, 22(4):bbaa256, 2020.

Ali Ezzat, Min Wu, Xiao-Li Li, and Chee-Keong Kwoh. Drug-target interaction prediction via class imbalance-aware ensemble learning. *BMC Bioinformatics*, 17(S19), December 2016. ISSN 1471-2105. doi: 10.1186/s12859-016-1377-y. URL http://dx.doi.org/10.1186/s12859-016-1377-y.

Shu-Cherng Fang and Jacob H.-S. Tsao. *Entropy Optimization: Shannon Measure of Entropy and its Properties*, pp. 916–921. Springer US, 2008. ISBN 9780387747590. doi: 10.1007/978-0-387-74759-0_161. URL http://dx.doi.org/10.1007/978-0-387-74759-0_161.

Moksh Jain, Tristan Deleu, Jason Hartford, Cheng-Hao Liu, Alex Hernandez-Garcia, and Yoshua Bengio. Gflownets for ai-driven scientific discovery. *Digital Discovery*, 2(3):557–577, 2023. ISSN 2635-098X. doi: 10.1039/d3dd00002h. URL http://dx.doi.org/10.1039/D3DD00002H.

M.L. Menéndez, J.A. Pardo, L. Pardo, and M.C. Pardo. The jensen-shannon divergence. *Journal of the Franklin Institute*, 334(2):307–318, March 1997. ISSN 0016-0032. doi: 10.1016/s0016-0032(96)00063-4. URL http://dx.doi.org/10.1016/S0016-0032(96)00063-4.

Nhat Khang Ngo, Truong Son Hy, and Risi Kondor. Predicting drug-drug interactions using deep generative models on graphs, 2022. URL https://arxiv.org/abs/2209.09941.

Andrei Cristian Nica, Moksh Jain, Emmanuel Bengio, Cheng-Hao Liu, Maksym Korablyov, Michael M. Bronstein, and Yoshua Bengio. Evaluating generalization in GFlownets for molecule design. In *ICLR2022 Machine Learning for Drug Discovery*, 2022. URL https://openreview.net/forum?id=JFSaHKNZ35b.

Julien Roy, Pierre-Luc Bacon, Christopher Pal, and Emmanuel Bengio. Goal-conditioned gflownets for controllable multi-objective molecular design, 2023. URL https://arxiv.org/abs/2306.04620.

Azmine Toushik Wasi, Taki Hasan Rafi, Raima Islam, Serbetar Karlo, and Dong-Kyu Chae. Cadgl: Context-aware deep graph learning for predicting drug-drug interactions, 2024. URL https://arxiv.org/abs/2403.17210.

David S Wishart, Yannick D Feunang, An C Guo, Elvis J Lo, Ana Marcu, Jason R Grant, Tanvir Sajed, Daniel Johnson, Carin Li, Zinat Sayeeda, et al. Drugbank 5.0: a major update to the drugbank database for 2018. *Nucleic acids research*, 46(D1):D1074–D1082, 2018.

Ziduo Yang, Weihe Zhong, Qiujie Lv, and Calvin Yu-Chian Chen. Learning size-adaptive molecular substructures for explainable drug–drug interaction prediction by substructure-aware graph neural network. *Chemical Science*, 13(29):8693–8703, 2022.

Yan Zhao, Jun Yin, Li Zhang, Yong Zhang, and Xing Chen. Drug–drug interaction prediction: databases, web servers and computational models. *Briefings in Bioinformatics*, 25(1):bbad445, 2023.