



Introduction to 'AI in drug discovery at ICANN2025'

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The 2nd Workshop on AI in Drug Discovery (<https://e-nns.org/icann2025/aidd>) was held within the 34th International Conference on Artificial Neural Networks (ICANN 2025) in Kaunas, Lithuania on September 11th 2025. It collected cutting-edge contributions in the rapidly evolving field of AI-driven drug discovery. Eleven papers were presented including a keynote, eight oral reports and two posters. Four articles presented at the Workshop are published in this themed collection of *Digital Discovery*, cited here as ref. 1–4. The main conference brought together about 200 participants and focused on various aspects of the application and theoretical development of AI and computational neuroscience, as well as their use across a wide range of scientific disciplines. We discuss the contributions and themes of the meeting below.

A platform for drug discovery targets (FRASE-bot) was presented as a keynote lecture by Dmitri Kireev.⁵ The platform operates by mining available 3D structures of ligand–protein complexes to

build a database of Fragments in Structural Environments (FRASE). Promising fragments are filtered using a graph neural network (GNN) and then scaled up to screen multi-billion-compound libraries. The authors use a contrastive neural network that maps 3D pharmacophores and ligands to a shared latent space to increase performance of their platform for screening of large libraries of compounds. Finally, the compounds are selected using a Hit-Triage Pretrained Transformer (Hit-TPT), which is used to estimate binding likelihood. The FRASE-bot successfully identified active hits for CACHE challenges by contributing winning solutions for some of the targets.⁵

Hit-TPT was developed to address issues with low accuracies of modern ML methods used to predict binding energies of ligands, which tend to occur due to unphysical predictions of binding poses. Uni-Mol Docking⁶ addressed this issue by leveraging pretrained molecular and pocket encoders trained on MOAD⁷ protein–ligand structures. The model takes a pocket and a compound's SMILES string as input to predict highly realistic 3D binding poses and achieve top scores for established benchmarks by eliminating steric clashes and chirality inversions which limit accuracies of previous methods.

A more practical case, focused on the design of molecules with antimicrobial

activity was considered by Olayo-Alarcon *et al.*⁸ The authors showed that including information about protein sequences of microbes (using protein clustering or pre-trained embeddings) significantly improved antimicrobial predictions over the one-hot encoding. This could potentially allow the development of faster therapies.

The generation of molecules with favourable ADME predictions is important for increasing the likelihood of designing novel drugs with good bioavailabilities. The ADMETrix platform⁹ used a set of more than 30 properties combined into a multi-objective reward function to iteratively steer molecular generation towards favorable drug-like profiles. The benchmarking of the platform and the presentation of an example case – the optimisation of diclofenac to reduce its hepatotoxicity while preserving its enzyme pocket binding affinity – exemplified the efficiency of the platform.

To ensure the efficiency of platforms such as ADMETrix, the modelling of ADMETox properties must be proven to be accurate and reliable. Nowadays, this is frequently achieved through representation learning models. NLP methods, such as those based on transformers architectures, are usually pre-trained on millions of chemical compounds, to increase their accuracy. However, up until now there has been no systematic

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study of how parameters of the pre-training (such as how many molecules should be used, how big the model should be, *etc.*) influence the model's accuracy. The MolEncoder^{4,10} closes this gap by systematically studying them and developing models with highest achieved accuracy for ADMETox properties.

Transformer models have found multiple applications in chemistry beyond property predictions. As an NLP method they are well suited for various translational tasks. Rajan *et al.*¹¹ compared the efficiency of translation of different linear string notations, SMILES, DeepSMILES, and SELFIES, to IUPAC names. Although these representations are interconvertible, SMILES achieved the highest accuracy. In the reverse translation, SELFIES achieved a marginally higher chemical validity but SMILES achieved a slightly better overall structural accuracy. Thus, the adequate selection of molecular representation is important for the modeling tasks. The transformer architecture is also the backbone of multiple LLMs such as GPT, where T stands for transformers.

The same author also presented MARCUS (Molecular Annotation and Recognition for Curating Unravelling Structures),¹ an open-source platform that extracts chemical information from PDF documents, which used GPT-4 for annotation of key entities and runs an ensemble of three optical chemical structure recognition (OCSR) engines to increase the accuracy of extraction of chemical structures. While LLMs can efficiently extract chemical data, such as reactions, from literature (and can even extract more reactions than using traditional software tools based on manually curated templates),¹² the computational cost associated with using them to analyse a large corpus of texts, such as patents, can be prohibitively high.

Vaškevičius and Kapociūtė-Dzikiene¹³ reported a cost efficient solution for the extraction of reactions by developing a classifier that first labels paragraphs as irrelevant, start, continuation, or end of a reaction. The labelled text is then processed by LLMs, with the top performing T5 model achieving 97% accuracy and up to 350 patents per hour processing speed on a single thread. The extracted

reactions are highly valuable for improving the accuracy of reaction predictions for retrosynthesis of molecules within the OCHEM-R platform,¹⁴ which uses a consensus of eight models to predict synthetic pathways.

In general, the explanation and interpretation of models using eXplainable AI (XAI) is critically important for drug discovery and computational toxicology, as they provide useful feedback to users by identifying sets of atoms which are contributing most to the target property. Benchmarking of several methods to interpret the NLP transformer CNN model showed a high consistency in identification of chemically correct structural motifs for prediction of functional groups and toxicity.³ However, with the addition of noise, the models' ability to identify motifs critically degraded due to the "explainability cliff", thus explaining the previous inconsistencies amid XAI explanations¹⁵ reported elsewhere.

Some of the methods, *e.g.* SHAP values, used in previous work, explain a model's predictions by assuming that the contribution of each atom to a target property is independent. However, for chemical structures, which are best represented as graphs, this assumption does not hold true since it does not consider structural constraints on the graph in molecules. The Myerson values calculate contributions of connected nodes (which form a coalition) thus operating directly on the graph's native node and edge features,² which is critically important for interpreting Graph Neural Networks (GNN). This feature allowed Myerson values to outperform the other nine state-of-the-art XAI methods for the most complex mutagenicity dataset for graph explanation accuracy metrics, and placed it among the top models for other datasets and metrics as summarised in the article.²

The training of GNNs is frequently subject to an "oversmoothing" problem, where information becomes overly averaged when passed through multiple message-passing layers. Smolyar addressed this problem by incorporating low-frequency eigenvectors/eigenmodes to capture richer topological structures,¹⁶ which led to a significant improvement in simulated physico-

chemical property prediction over the baseline model.

The workshop successfully achieved its overarching aim of bringing together machine learning experts, computational chemists and cheminformatics working on the development and application of ML in chemistry. The variety of topics reflects the expanding role of advanced ML in chemistry and in particular of modern methods such as transformers and GNNs, which is in line with the conclusions of the Tox24 challenge, where the high accuracy of such methods for the prediction of toxicological endpoints was demonstrated.¹⁷ Model explainability is another important direction of research, since providing scores alone does not sufficiently qualify a model's predictions enough to make them actionable, particularly in areas such as drug discovery and computational toxicology. The explainability of models is an important source of feedback, to guide the design of new molecules or provide mechanistic interpretations of a compound's mechanism of action (MOA).

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