AACR American Association for Cancer Research®
ANNUAL MEETING 2025 CHICAGO
APRIL 25–30
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DEL-AI: Proteome-Wide *In Silico* Screening of Multi-Billion Compound Libraries Using Machine Learning Foundation Models

Paul Novick, PhD
Nurix Therapeutics, San Francisco, CA

NURIX

Disclosure Information

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Paul Novick

I have the following relevant financial relationships to disclose:

Employee of: Nurix Therapeutics

Stockholder in: Nurix Therapeutics

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Small Molecule Drug Discovery Begins with a Binder

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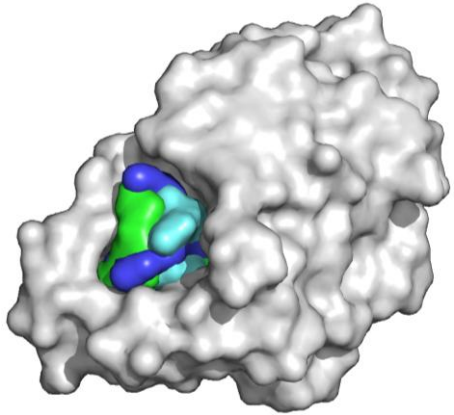
Lead Identification is a central challenge in small molecule drug discovery

How can this be done efficiently for novel therapeutic targets?



- Fragment Screening
- High Throughput Screening (HTS)
- Virtual Screening
- DNA Encoded Libraries (DEL)
- DEL + Machine Learning (DEL AI)

Library Size (Log10)

DEL is a Productive Lead ID Technology Generating Massive Datasets

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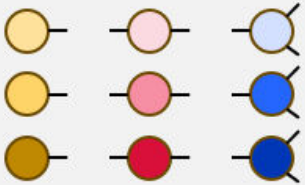
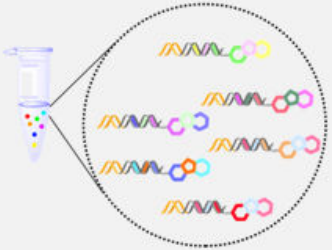
DEL Libraries

1000's of Building Blocks

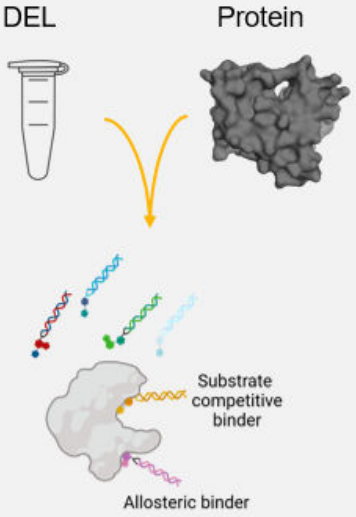


Combinatorial Synthesis



Over 5 Billion DEL Ligands

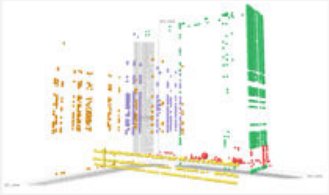
DEL Screening

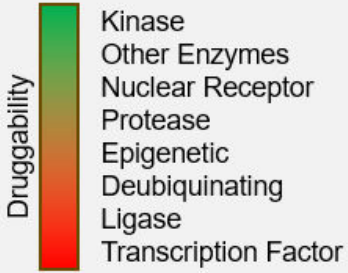


Over 6 Trillion DEL Datapoints

DEL Hit Validation

Ligand Selection and Confirmation





Over 60 High Affinity Series

A Primer on DEL Data Interpretation

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When reviewing DEL data in a Cube representation, we are looking for structural patterns in the data.

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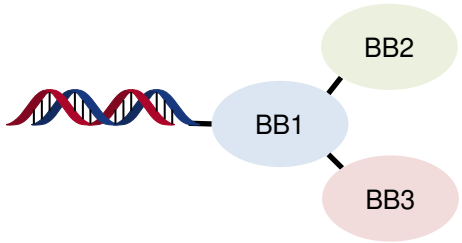

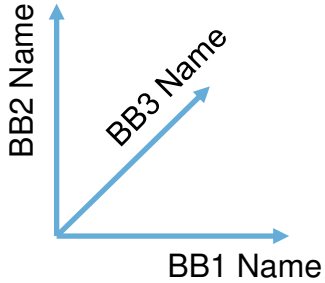

BB = chemical Building Block

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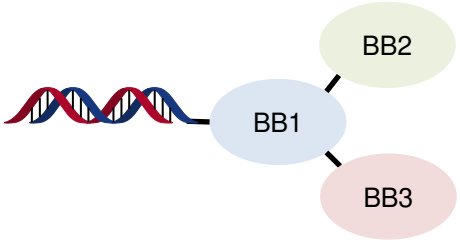
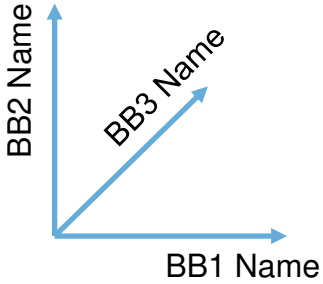
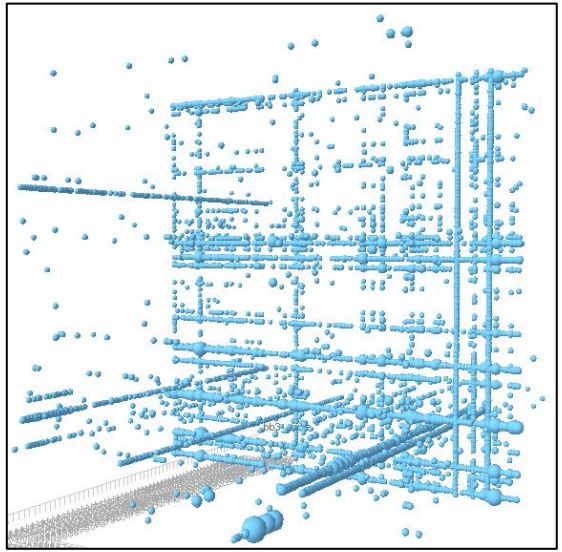




The Cube



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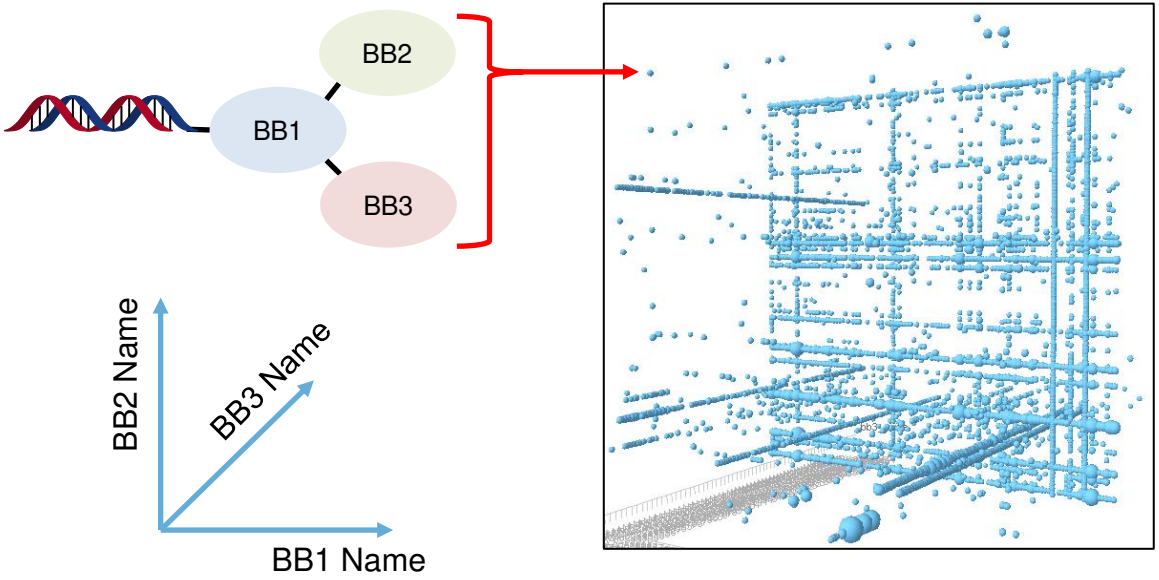

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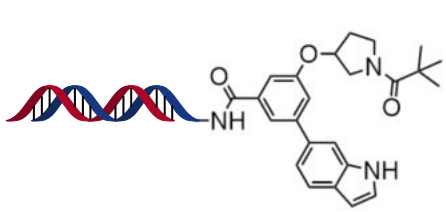

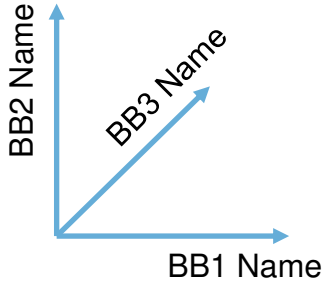

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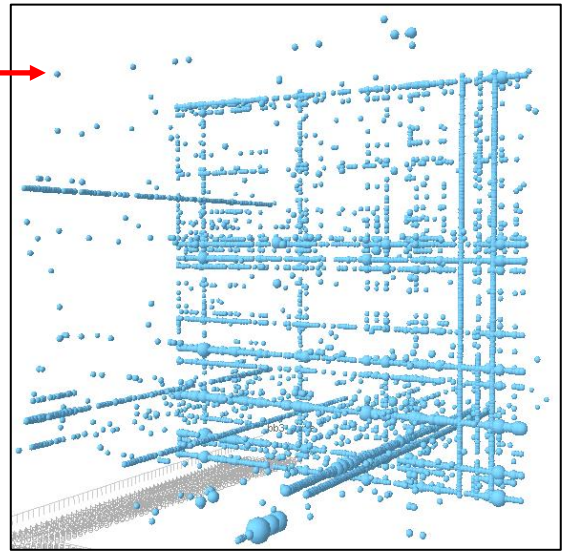

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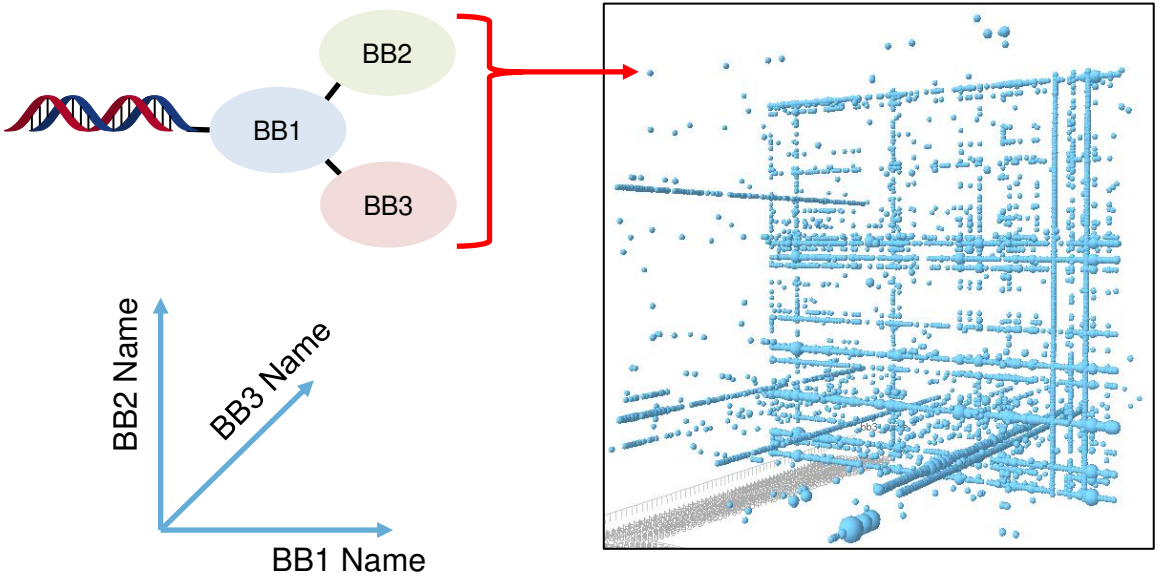

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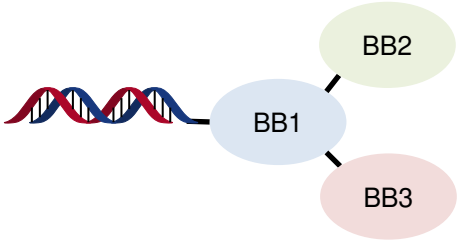

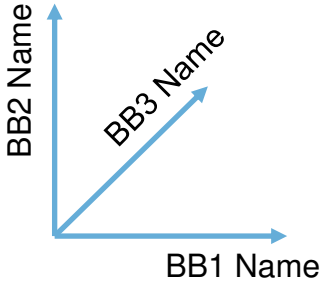

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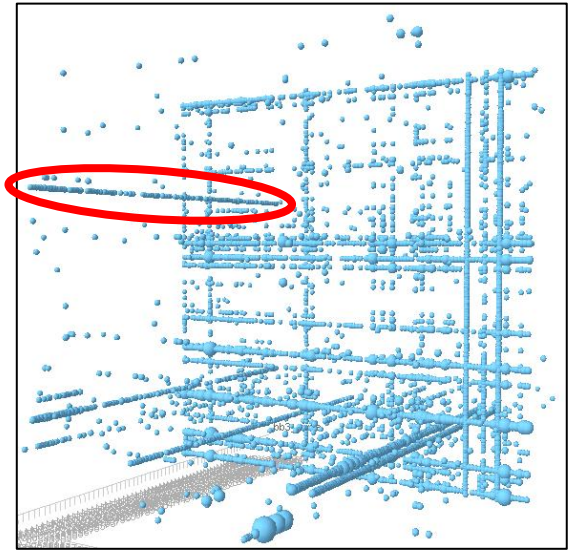
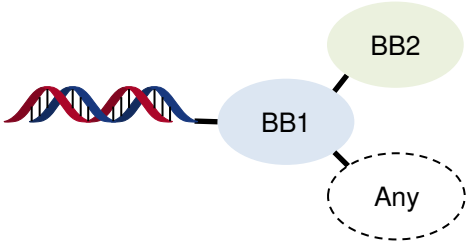


Lines: 2 shared building blocks



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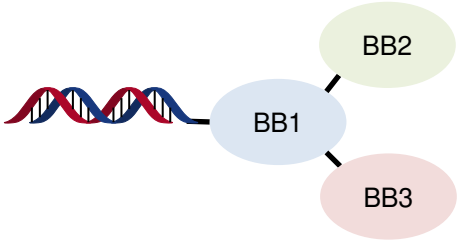

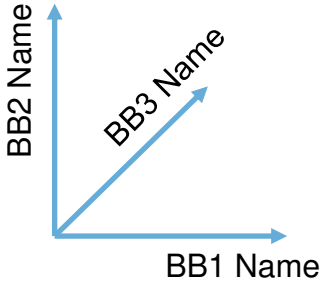

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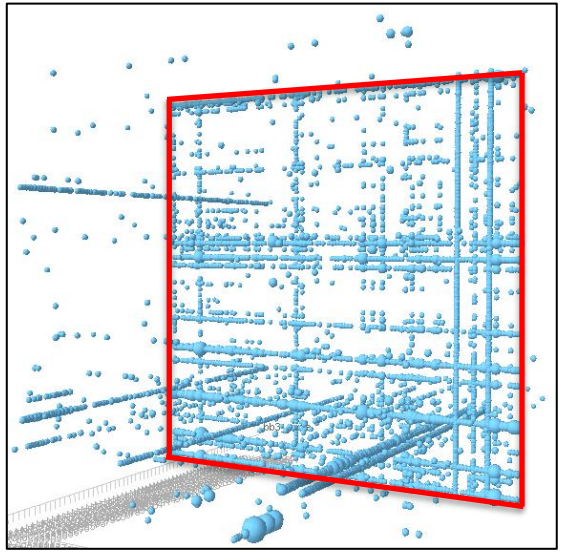
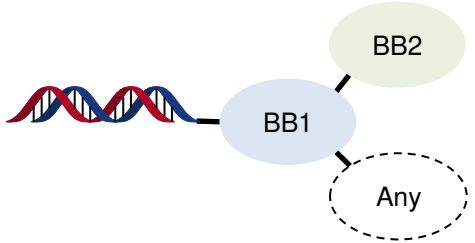
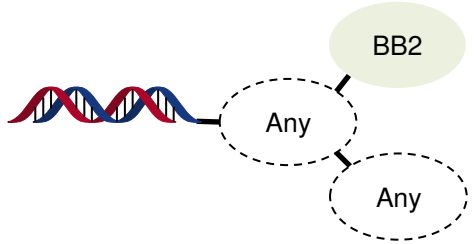


Lines: 2 shared building blocks



Planes: 1 shared building block



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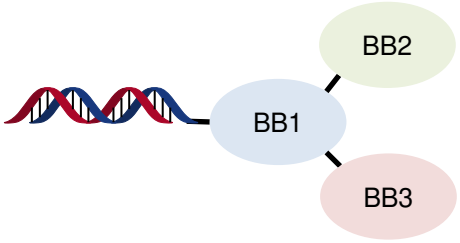

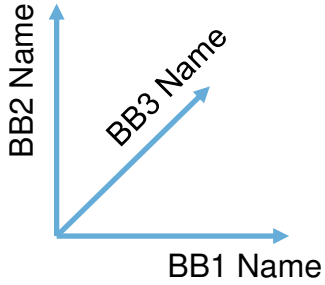

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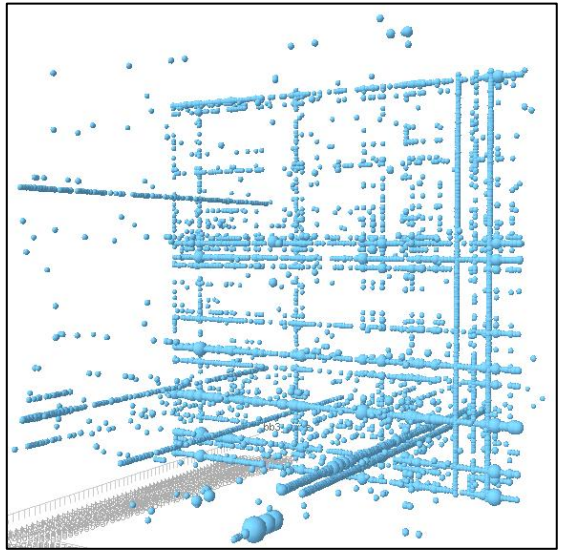

In comparing two sets of DEL data, we evaluate the similarity of these patterns.

DEL Foundation is a Generalized Model Able to Prospectively Predict DEL Data

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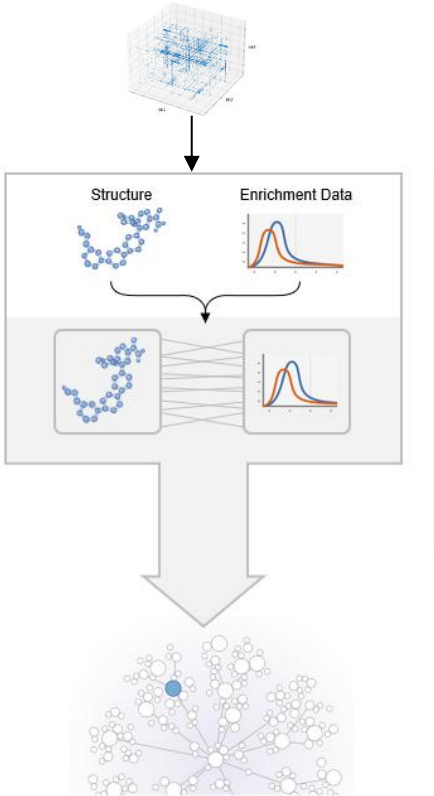
Traditional DEL ML Approaches

- Established DEL ML approaches train models on single target datasets
- These models predict binding to a single protein and are inefficient to scale to ligand discovery across diverse targets
- Rely on time and resource intensive quality protein production and DEL screen execution.



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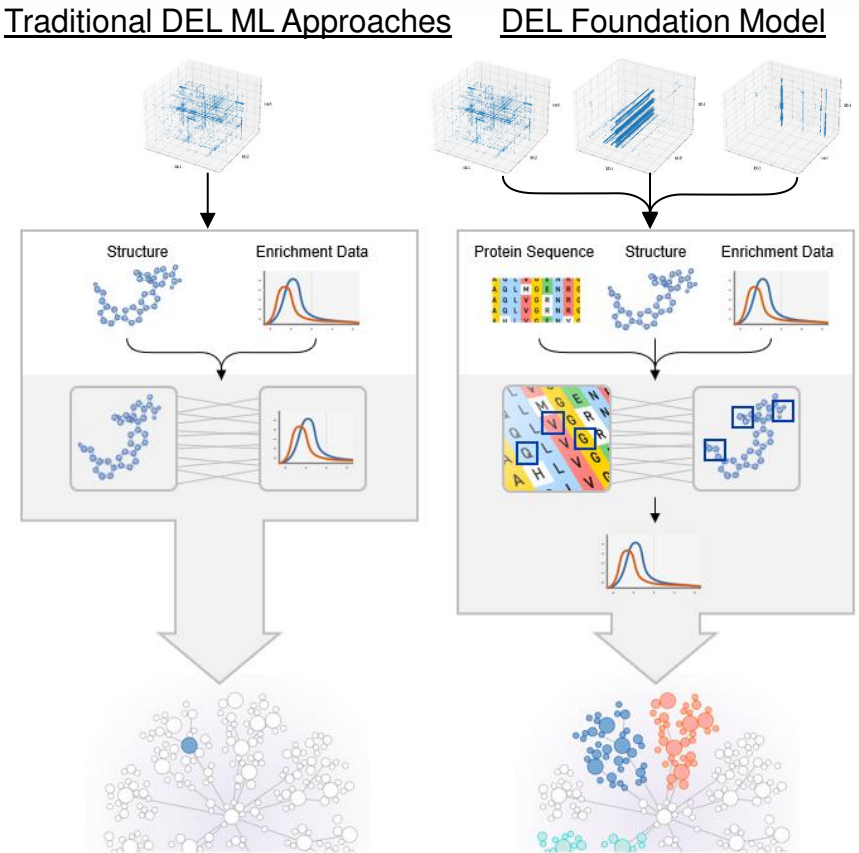

- DEL Foundation Model is trained on DEL datasets from diverse protein targets
- These models learn a generalized relationship between protein sequence and molecular structure
- DEL Foundation is thus able to predict DEL data on proteins without the need for experimental data

DEL Foundation Enables Efficient Ligand ID for Unseen Targets

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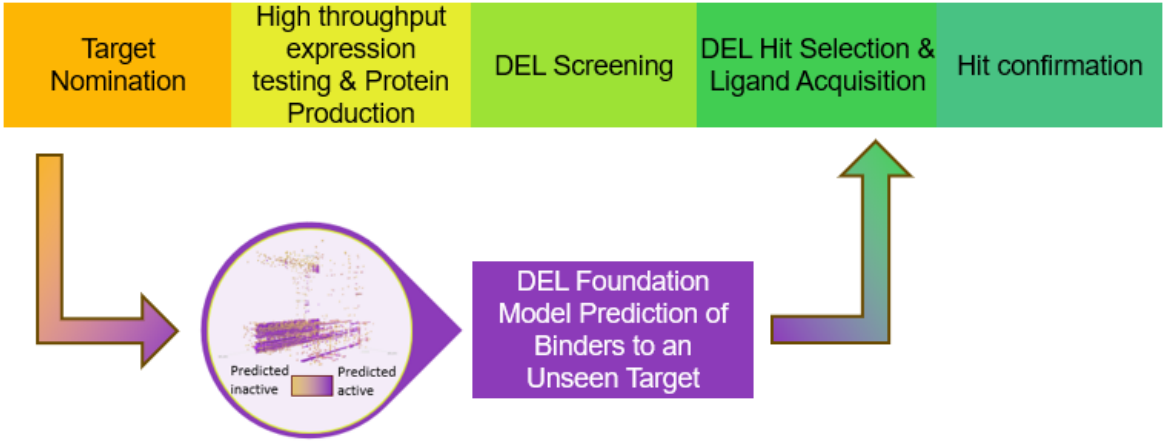
DEL Foundation-based Lead ID bypasses multiple resource intensive processes and unlocks targets which are otherwise “un-DEL-able”



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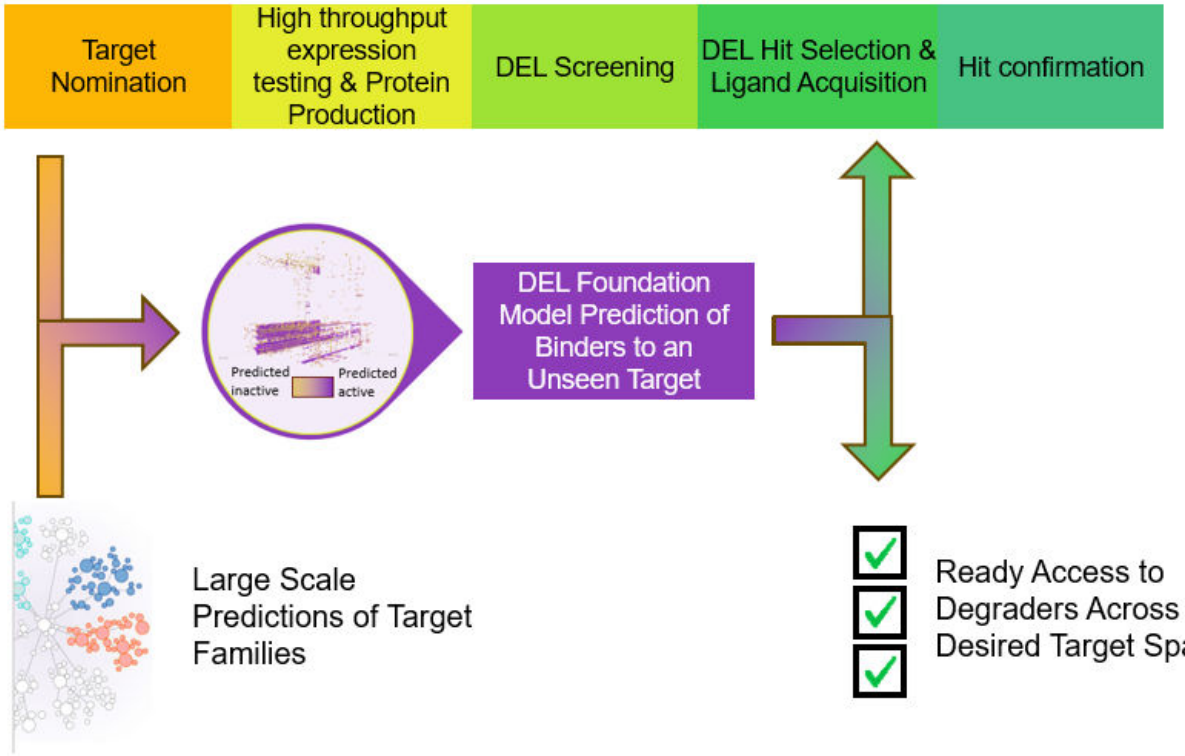
DEL Foundation-based Lead ID bypasses multiple resource intensive processes and unlocks targets which are otherwise “un-DEL-able”

DEL Foundation models allow access to broad swaths of the proteome



DEL Foundation Leverages Nurix's Proprietary and Highly Ordered Datasets

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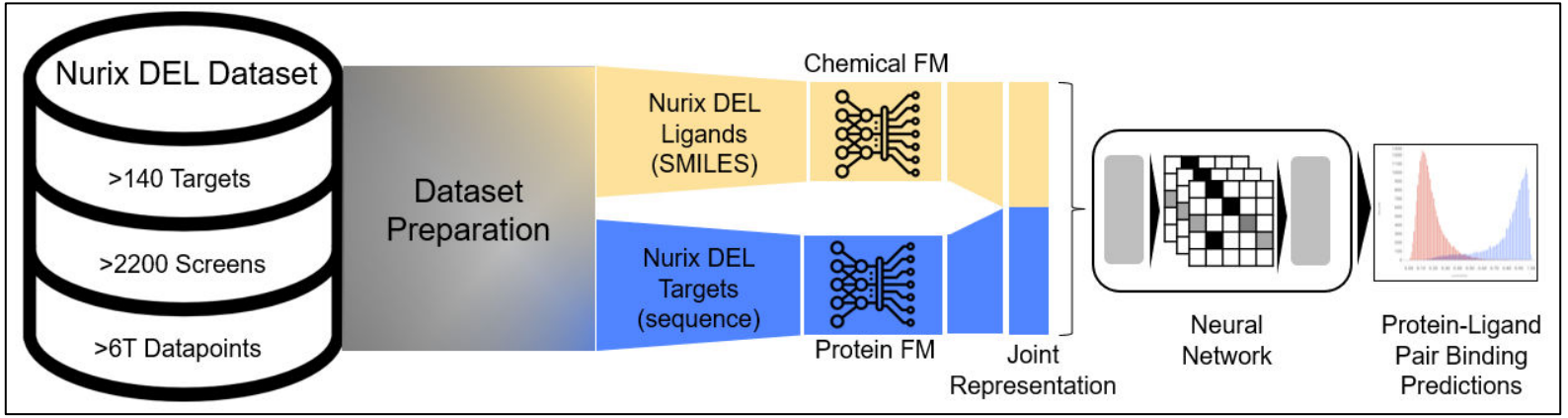
Collaboration between Nurix, Loka Inc., and Amazon Web Services



Schematic of Data Processing and Model Architecture

DEL Foundation Dataset Construction and Definition of Terms

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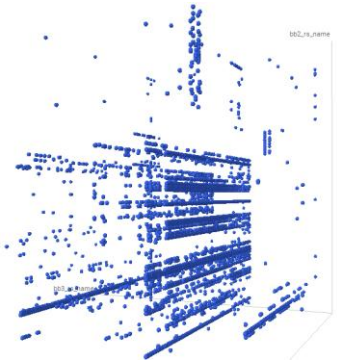
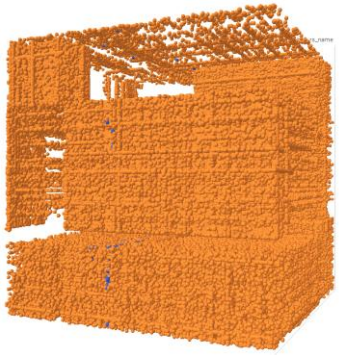
Retrospective datasets constructed from experimental data



<u>Experimental Actives</u>
Ligands enriched in the DEL screen



<u>Experimental Inactives</u>
Ligands which did not enrich in the DEL screen, sampled from full DEL library

DEL Foundation Dataset Construction and Definition of Terms

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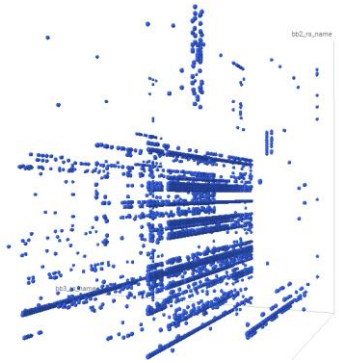
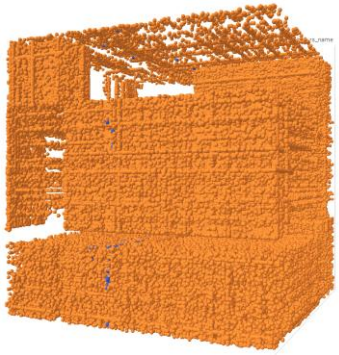
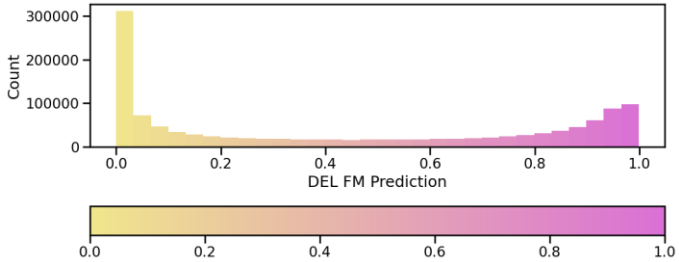




Datasets not in the training dataset are evaluated by DEL Foundation (DEL FM)



Experimental Actives
Ligands enriched in the DEL screen

Experimental Inactives
Ligands which did not enrich in the DEL screen, sampled from full DEL library

DEL FM Inactives
Ligands predicted as non-binders (low DEL FM score)

DEL FM Actives
Ligands predicted as binders (high DEL FM score)

Different Lenses on Prospective DEL Foundation Predictions

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Can DEL Foundation prospectively predict binders for new proteins?

- Novel Constructs
- Novel Target Forms
- Novel Targets

Can DEL Foundation prospectively predict binders from new libraries?

High Accuracy Predicting Experimental Data on New Constructs

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Binders predicted by DEL Foundation align closely to experimental data for a novel construct outside the training dataset.

Constructs in Training

His-Avi-[POI trunc]

Avi-[POI trunc]

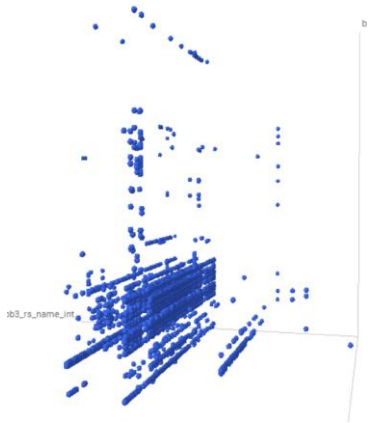
Avi-[POI FL]-His

Constructs in Holdout

[POI trunc]-Avi

POI = Protein Of Interest

Experimental Actives



High Accuracy Predicting Experimental Data on New Constructs

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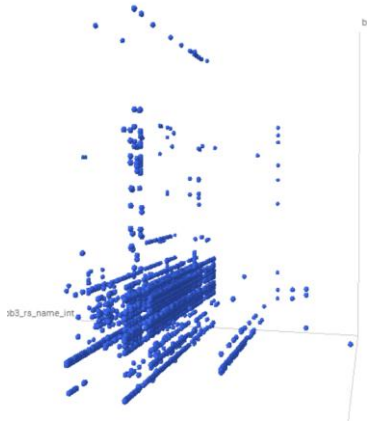
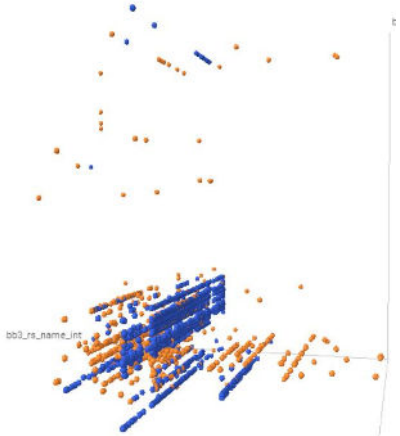


DEL FM Actives with Experimental Annotation



Experimental Actives
Experimental Inactives

High Accuracy Predicting Experimental Data on New Target Forms

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Binders predicted by DEL FM largely recapitulate experimental data of a protein complex. Additionally, DEL FM ignores an experimentally observed plane considered promiscuous.

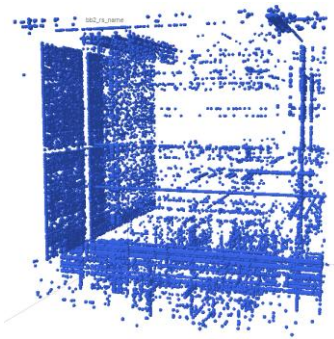
Target Form in Training

6H-Avi- POI trunc

Target Form in Holdout

Avi- POI FL BP

Experimental Actives



POI = Protein Of Interest
BP = Binding Partner

High Accuracy Predicting Experimental Data on New Target Forms

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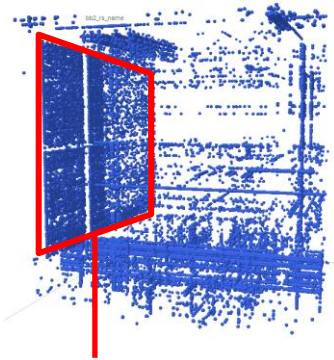

Plane of promiscuous binders

POI = Protein Of Interest
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High Accuracy Predicting Experimental Data on New Target Forms

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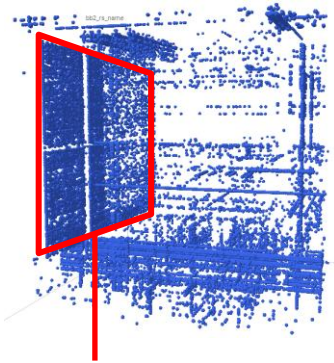
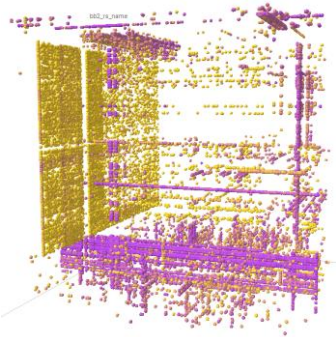


Plane of promiscuous binders

DEL FM Scoring of Experimental Actives



0 1
DEL FM Score

POI = Protein Of Interest
BP = Binding Partner

High Accuracy Predicting Experimental Data on New Target Forms

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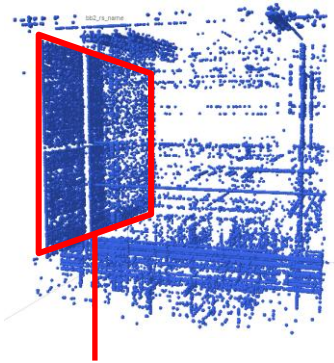
Experimental Actives



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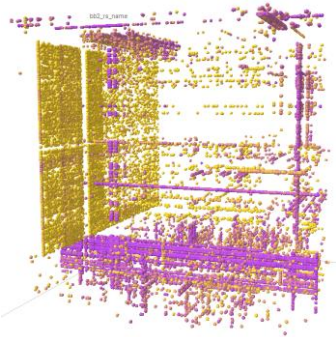
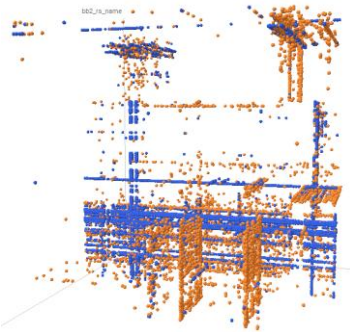


0 1
DEL FM Score

DEL FM Actives with Experimental Annotation



Experimental Actives
Experimental Inactives

POI = Protein Of Interest
BP = Binding Partner

DEL Foundation Identifies Confirmed Binders from High Background Screen

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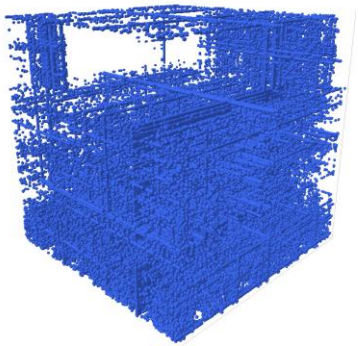
DEL FM predicts subset of experimental signal, inclusive of confirmed ligands.

Target Forms in Training

Targets in Holdout

Experimental Actives



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DEL Foundation Identifies Confirmed Binders from High Background Screen

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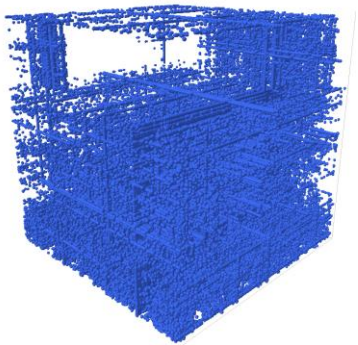

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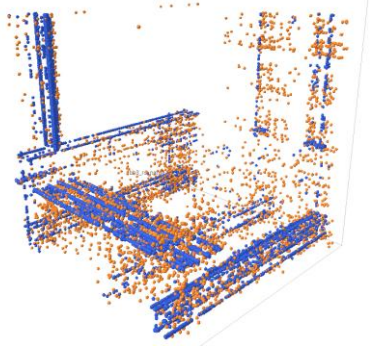

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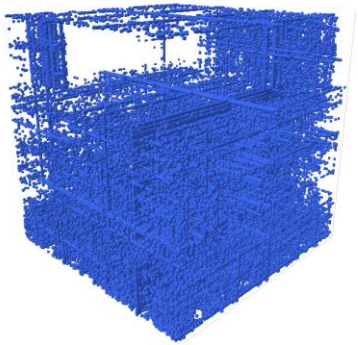

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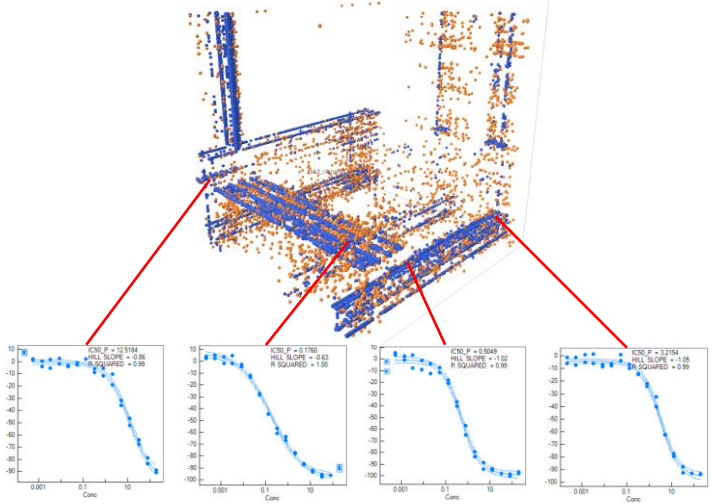

Predicting Small Molecule Binders to Novel Proteins Beyond Training Data

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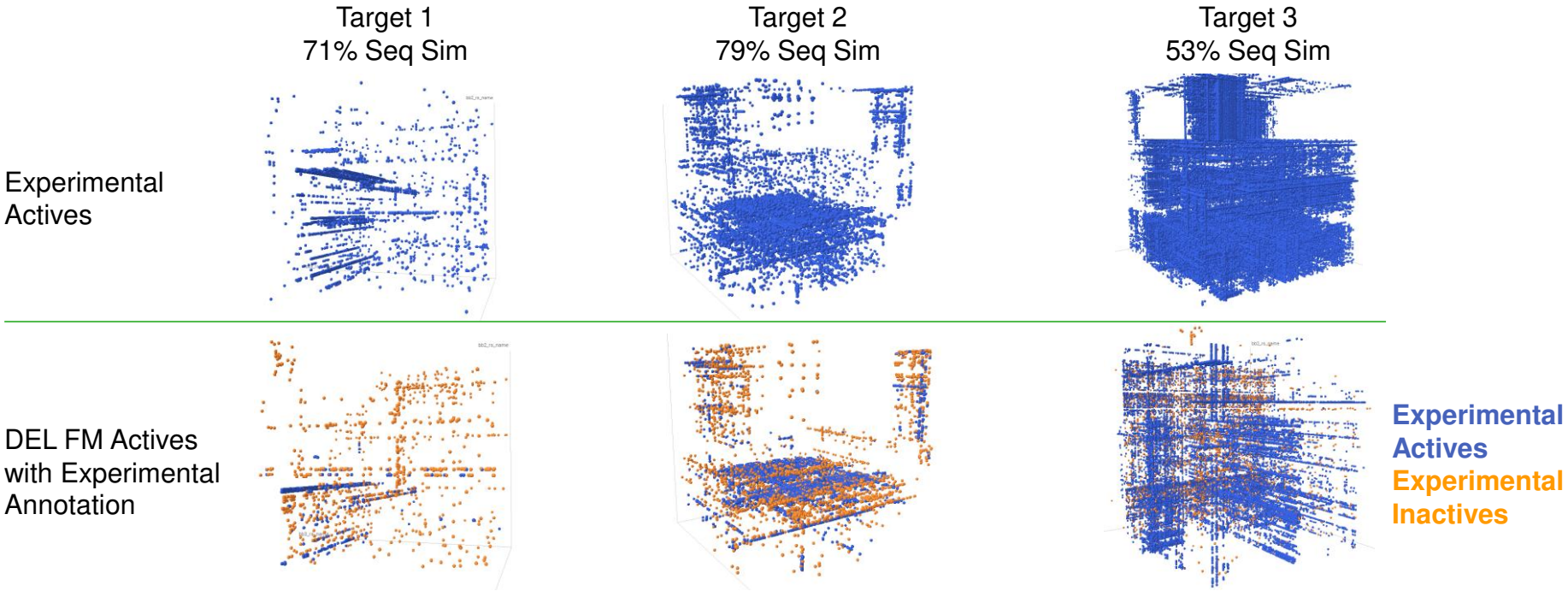
DEL Foundation predicts most dominant patterns in experimental data despite low sequence similarity of query proteins to those in the training set.



Performance of DEL FM Correlates with Sequence Similarity

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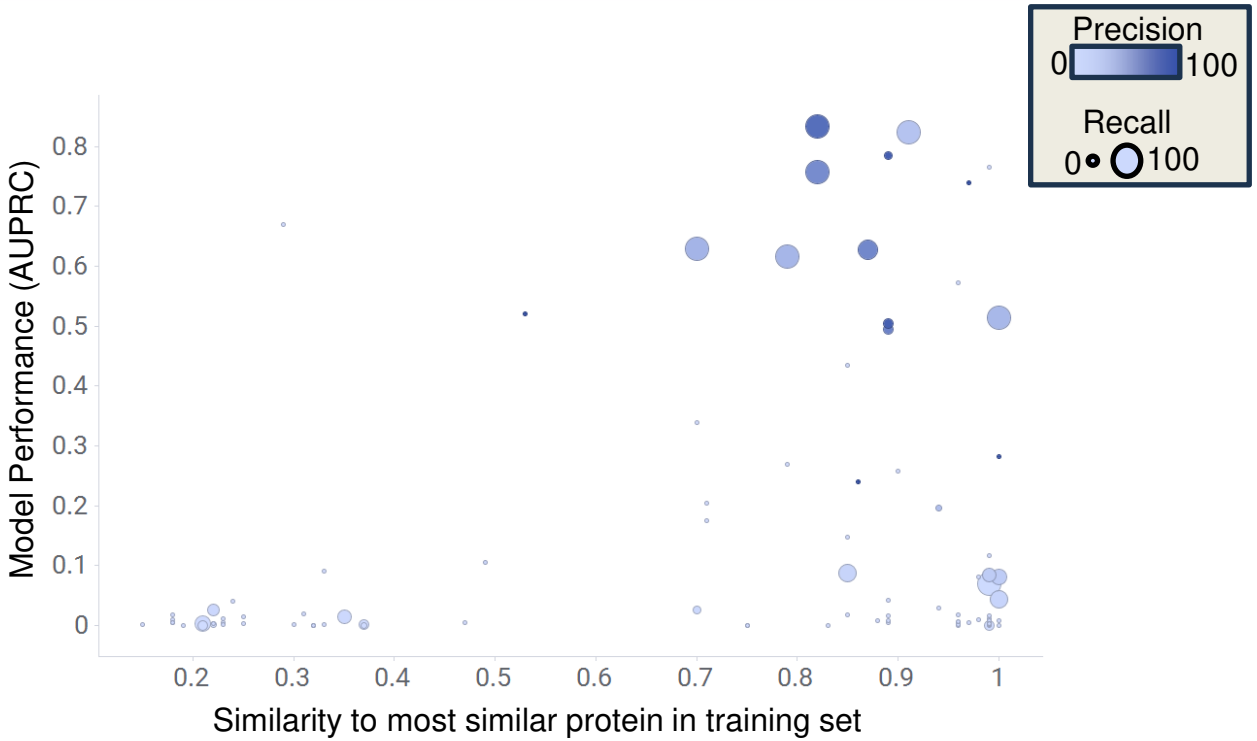

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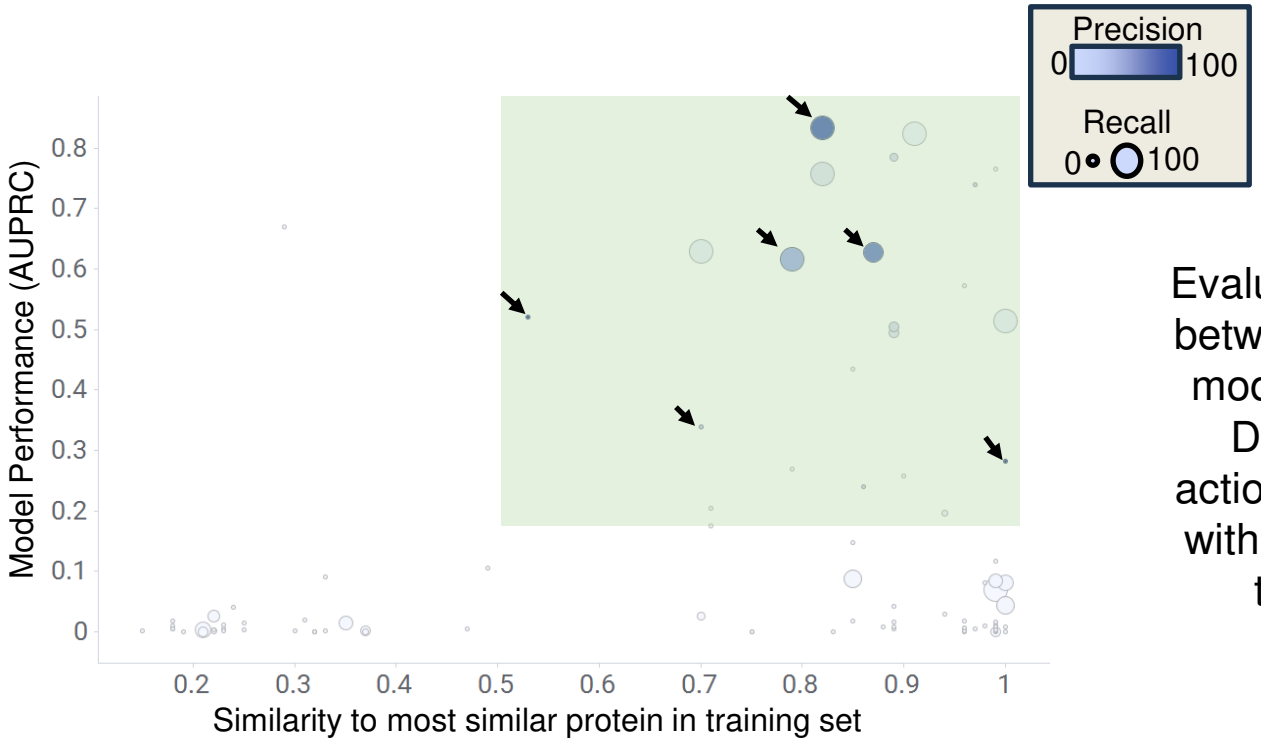

Evaluating the global relationship between sequence similarity and model performance, we expect DEL Foundation to provide actionable predictions for targets with as low as 0.5 similarity to a target in the training set.

Different Lenses on Prospective DEL Foundation Predictions

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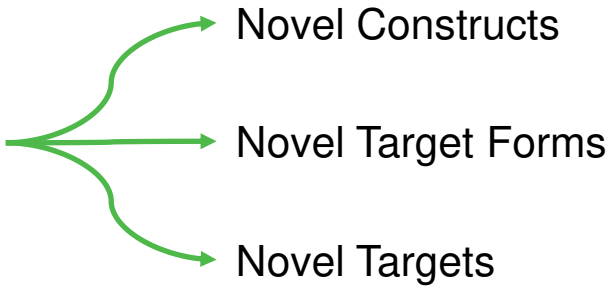
Can DEL Foundation prospectively predict binders for new proteins?



Can DEL Foundation prospectively predict binders from new libraries?

DEL Foundation Can Predict Binders from Libraries Beyond Training Set

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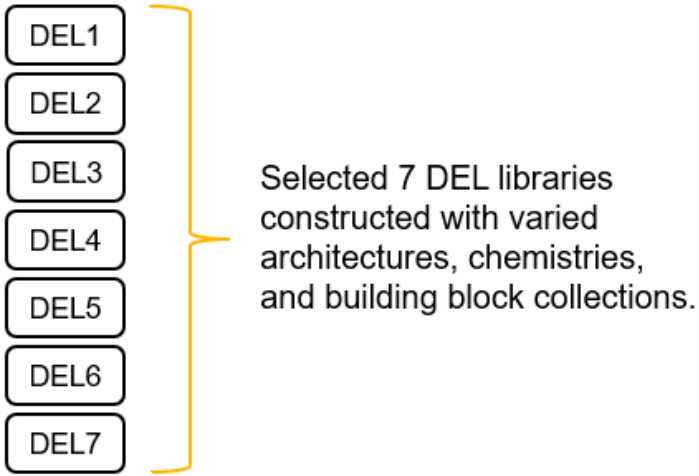
ML models that can generalize to new chemical space expand application scope, especially towards use for Lead Optimization.

A recent public competition was unable to make predictions for libraries outside the training set.[1] We tested the ability of DEL FM to succeed on this task.

LOO* Experimental Design



*LOO = Leave One Out

[1] Blevins, A; BELKA; NeurIps, 2024

DEL Foundation Can Predict Binders from Libraries Beyond Training Set

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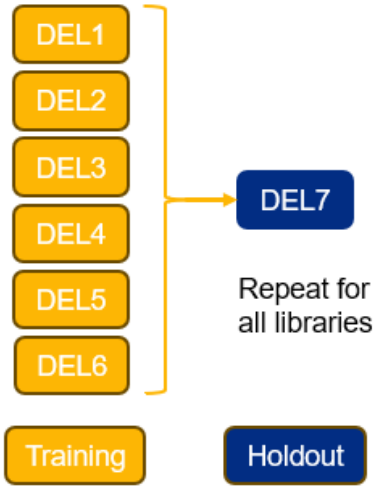
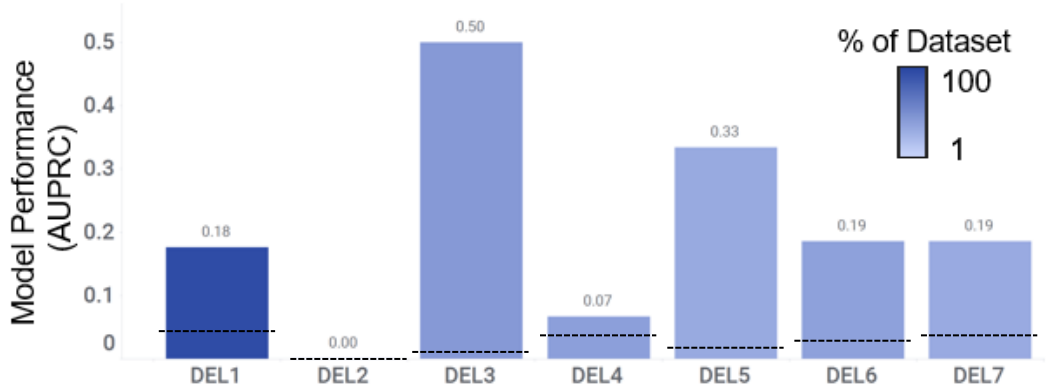


Holdout Predictions



	DEL1	DEL2	DEL3	DEL4	DEL5	DEL6	DEL7
Random Chance	.05	.00	.01	.04	.02	.03	.04

Diversity of DEL Libraries in Foundation Model Training Set

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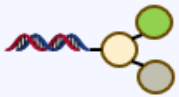
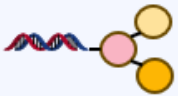
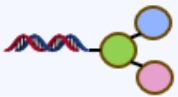
Analysis of libraries in training set demonstrates structural diversity consistent with design

Library	% of Dataset	Architecture
DEL1	72%	
DEL2	1%	
DEL3	7%	
DEL4	6%	
DEL5	4%	
DEL6	6%	
DEL7	4%	

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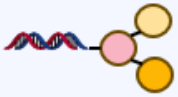
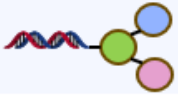
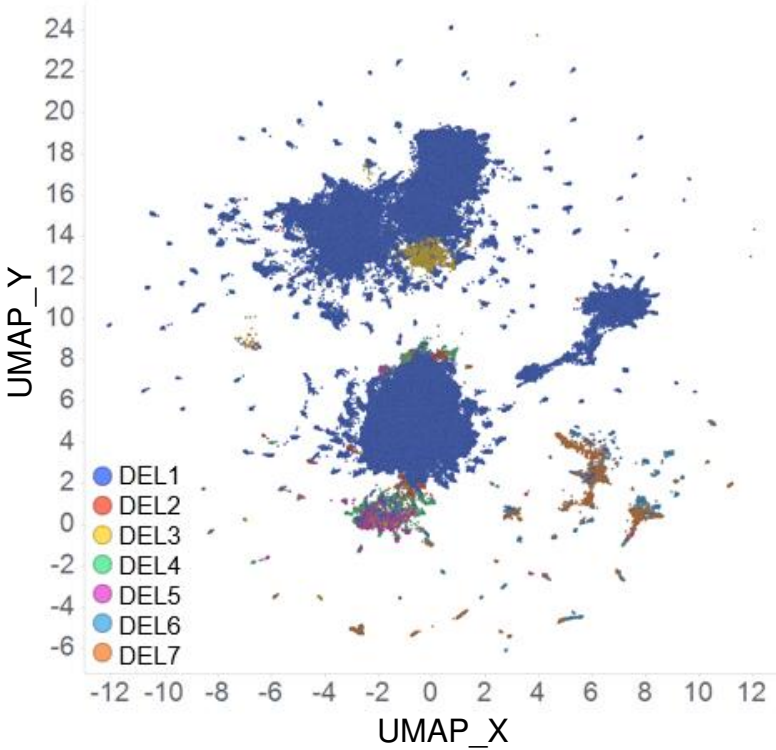
DEL6	6%	
DEL7	4%	



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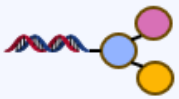
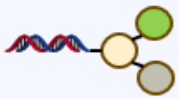
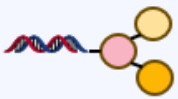
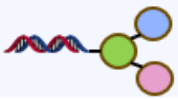
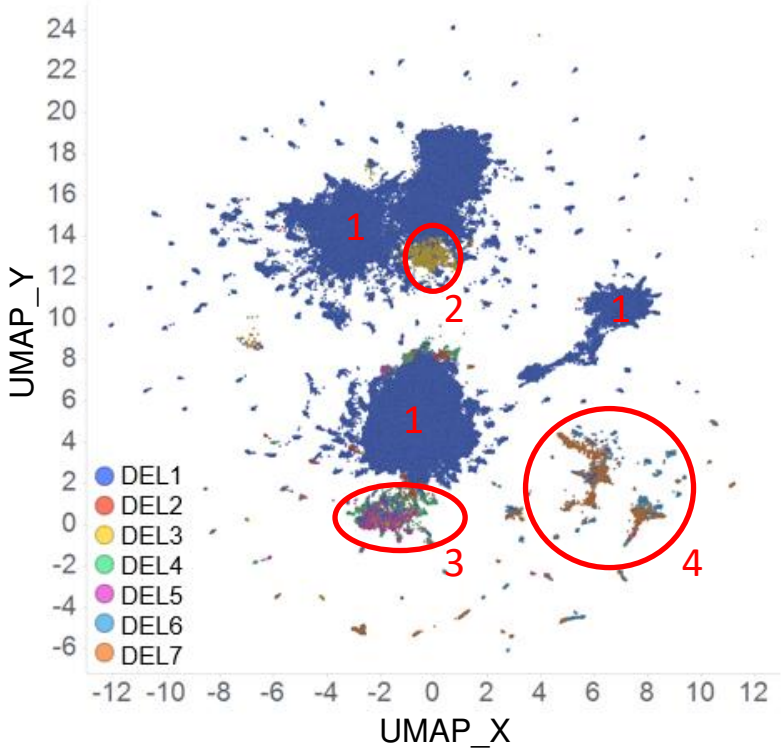
DEL3	7%		Group 2
DEL4	6%		Group 3
DEL5	4%		
DEL6	6%		Group 4
DEL7	4%		



Diversity of DEL Libraries in Foundation Model Training Set

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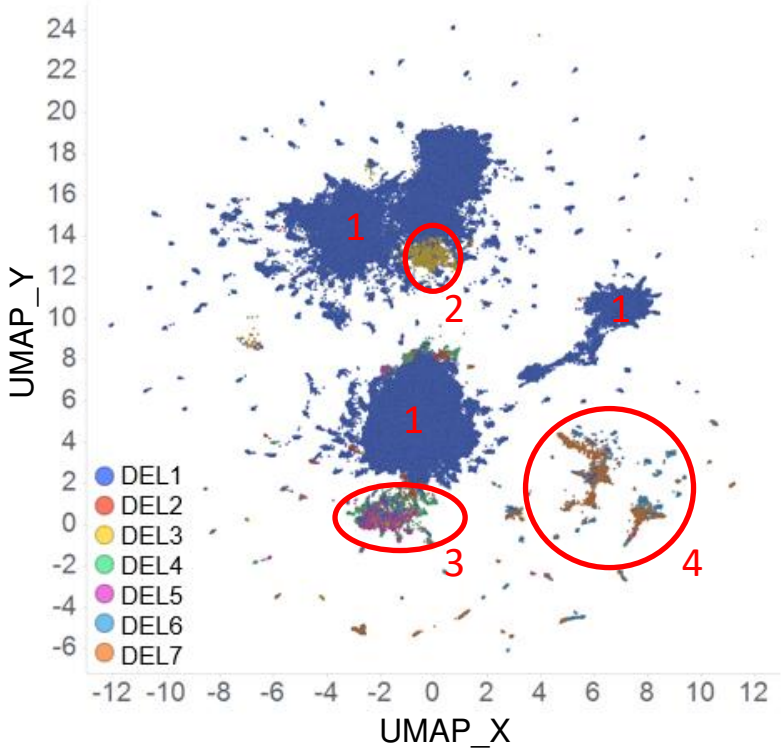
DEL FM predicts binders from unseen libraries representing distinct regions of chemical space



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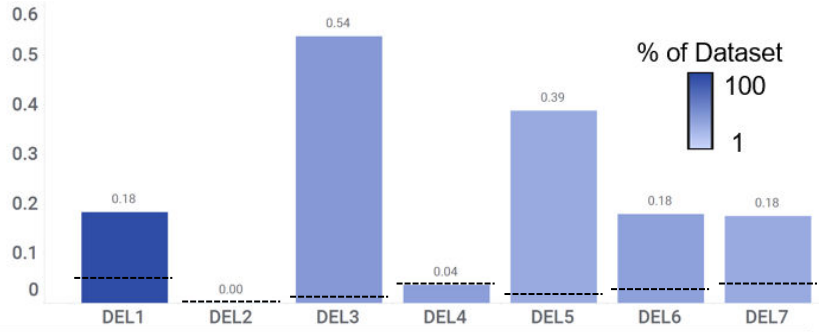
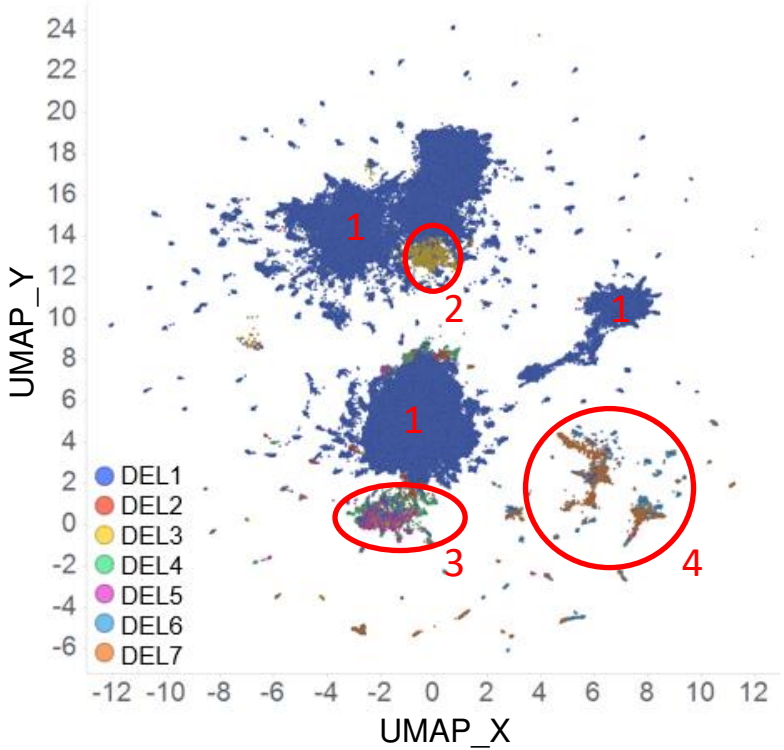
Holdout Predictions



	DEL1	DEL2	DEL3	DEL4	DEL5	DEL6	DEL7
Random Chance	.05	.00	.01	.04	.02	.03	.04



Continued Development of DEL FM Addresses Realities of Experimental DEL

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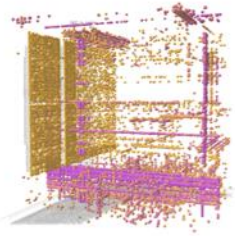
Insufficient Metrics for Evaluating Model Performance

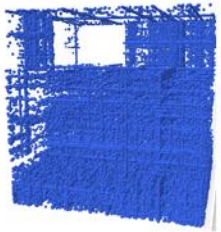
Is a model which fully recapitulates experimental data the goal?

If not, how should we measure performance?

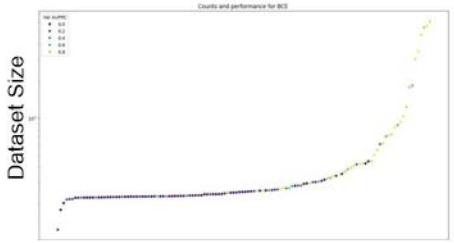
Experimental FP



Experimental Background



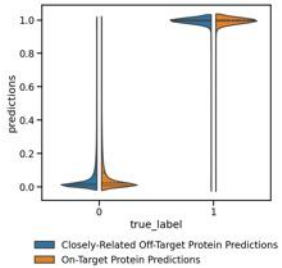
Heterogeneous Datasets Affect Model Learnings



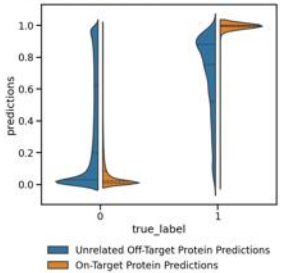
DEL Datasets are very heterogeneous in size which can impact the model's ability to learn from the full diversity of targets in the training set.

Data Sampling Encourages Shortcut Learning

Predicting **Protein X** dataset vs **Close Homologue** sequence

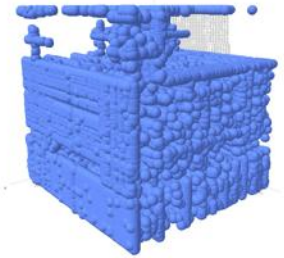


Predicting **Protein X** dataset vs **Distantly-Related** sequence



High Background of False Positives on Full Library Predictions

Huge size of DEL collections results in high background even with extreme precision.



Summary

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- DEL Foundation is a first-in-class ML model able to prospectively predict DEL data
- DEL Foundation predicts DEL data for novel protein targets with performance correlated with similarity of the query protein sequence to training data
- DEL Foundation generalizes to unseen DEL libraries and unseen chemical space
- DEL Foundation transforms the scale and approach of Lead ID at Nurix

Acknowledgments

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