Accurately Predicting Functional Fully Modified siRNAs with Advanced Machine Learning Techniques

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Introduction

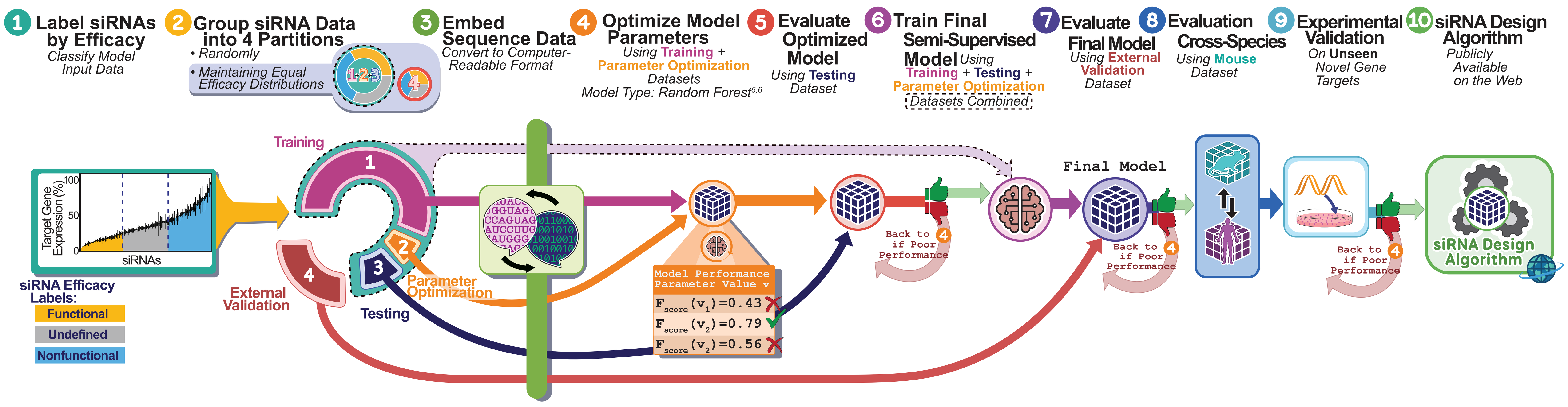
Problem: identifying potent therapeutic fully-modified siRNAs

- To be therapeutically active siRNAs must be fully modified[1]
- Existing methods for designing native siRNAs are not predictive for therapeutic, fully modified siRNAs[2]
- Both RISC (RNA induced silencing complex) interactions and target specific context define siRNA efficacy[2]
- Target specific features are not well defined for therapeutic siRNAs

Goal: develop algorithm to identify potent therapeutic siRNAs

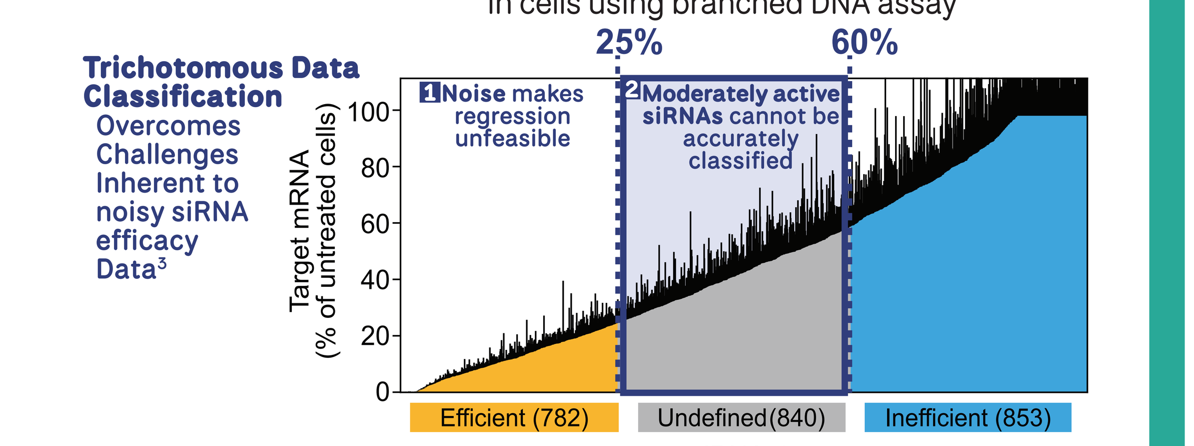
- Apply 1 large (**~5000 siRNAs**) therapeutic fully modified data-set to explore 2 target gene-aware real world design task 5
- Employ AI methods: 3 **deep learning**-based sequence embedding and 6 **semi-supervised learning** to capture both RISC and target-driven elements
- 7 markedly enhance prediction in 8 **species-specific** manner
- 4 Optimize & 9 **experimentally-validate** model on therapeutic design task across disease-relevant target genes
- Deploy 10 **siRNA Design Algorithm** as an easy-to-use **Web Portal** free for academic use[3,4]

Procedure for Building and Optimizing siRNA Efficacy Prediction Model

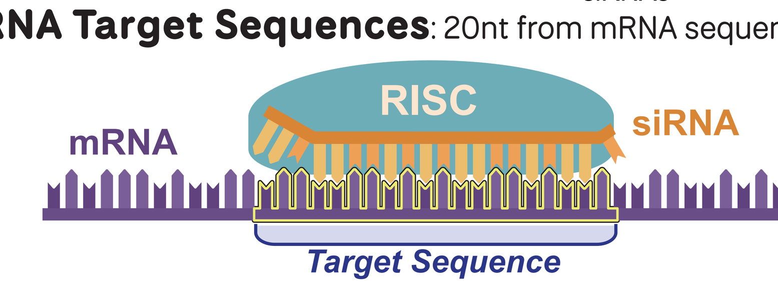


1 Data Used to Build Model

1 siRNA Efficacy Data: endogenous transcript knockdown evaluated in cells using branched DNA assay

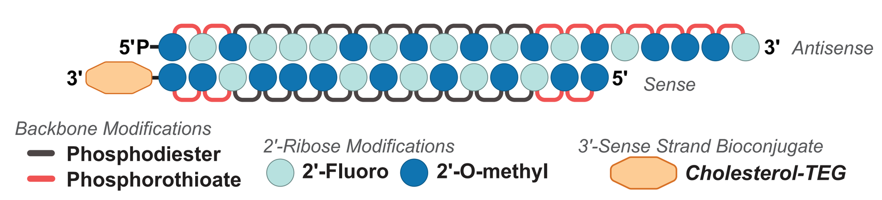


2 siRNA Target Sequences: 20nt from mRNA sequence



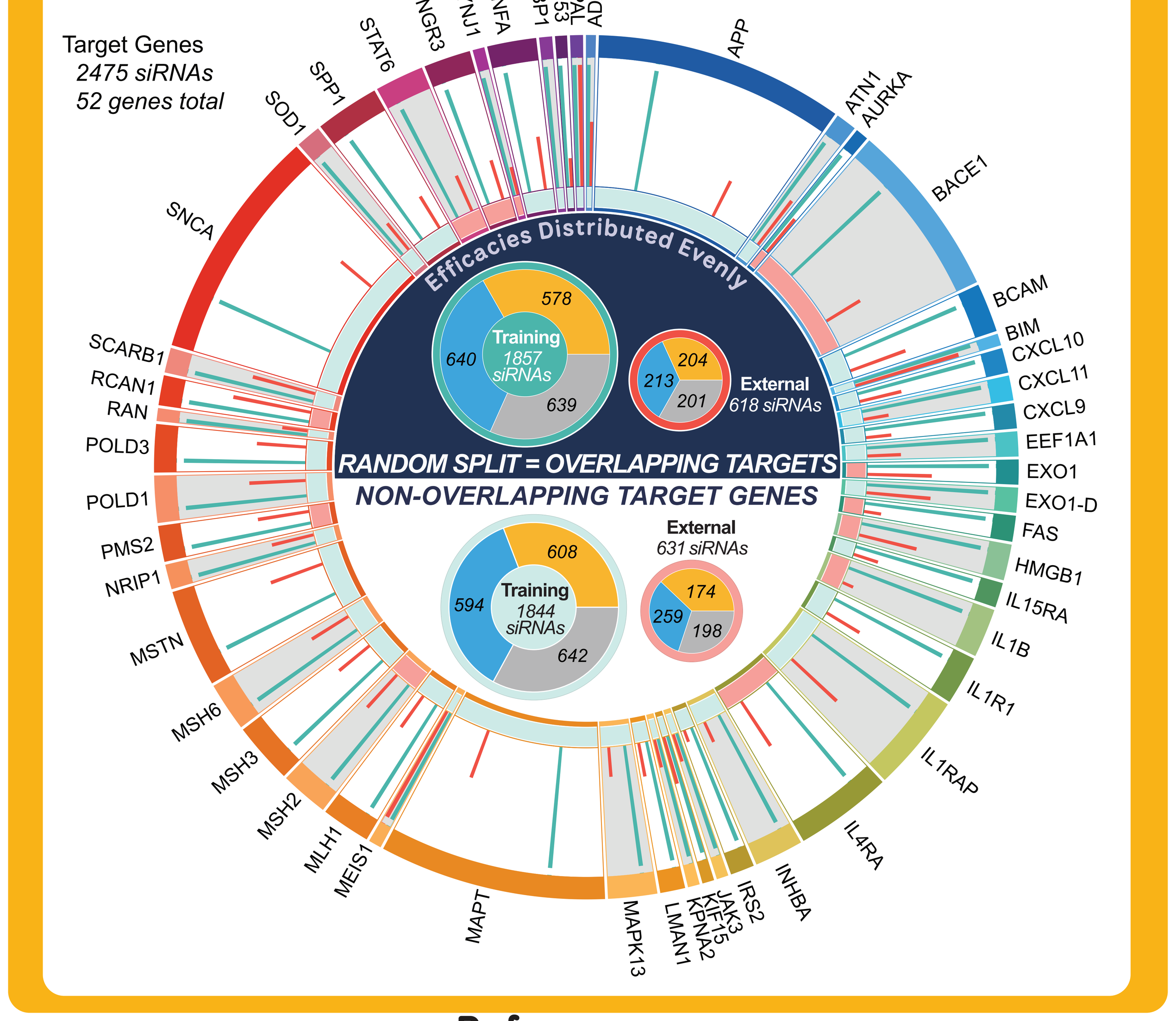
*2475 human siRNAs (shown), 2865 mouse, 5340 total

Chemical Scaffold of Fully Modified Therapeutic siRNA



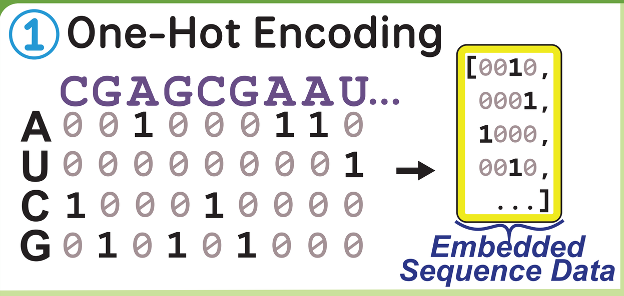
2 Data Partitioning: Random vs. by Target Gene

Target Gene split evaluates real-world siRNA design task

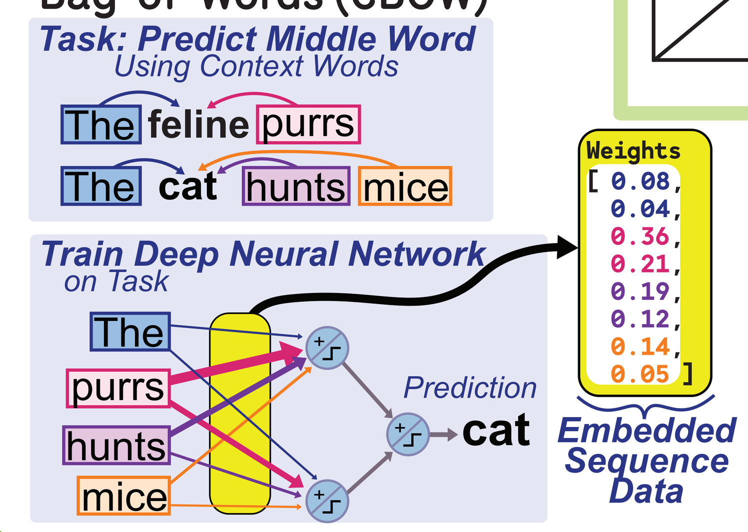


3 Sequence Feature Embedding Methods Significantly Impact Model Predictive Power

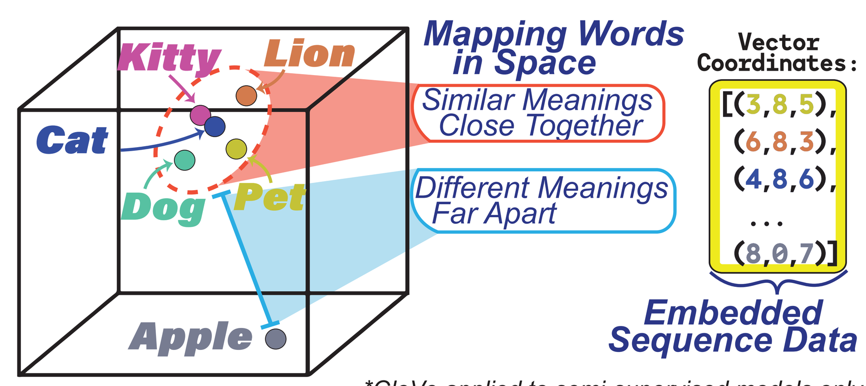
1 One-Hot Encoding



2 Deep Continuous Bag-of-Words (CBOW)[7]

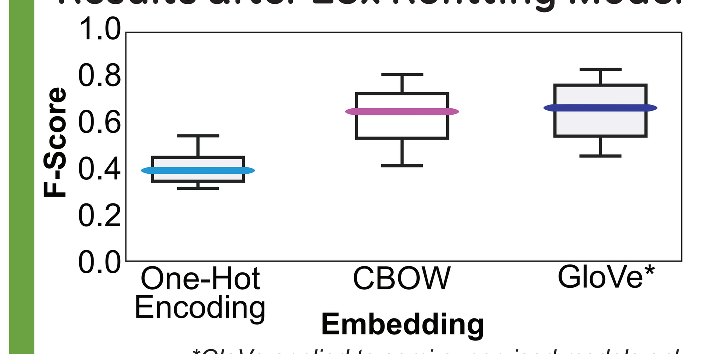


3 Global Vector Embedding[8]* (GloVe)



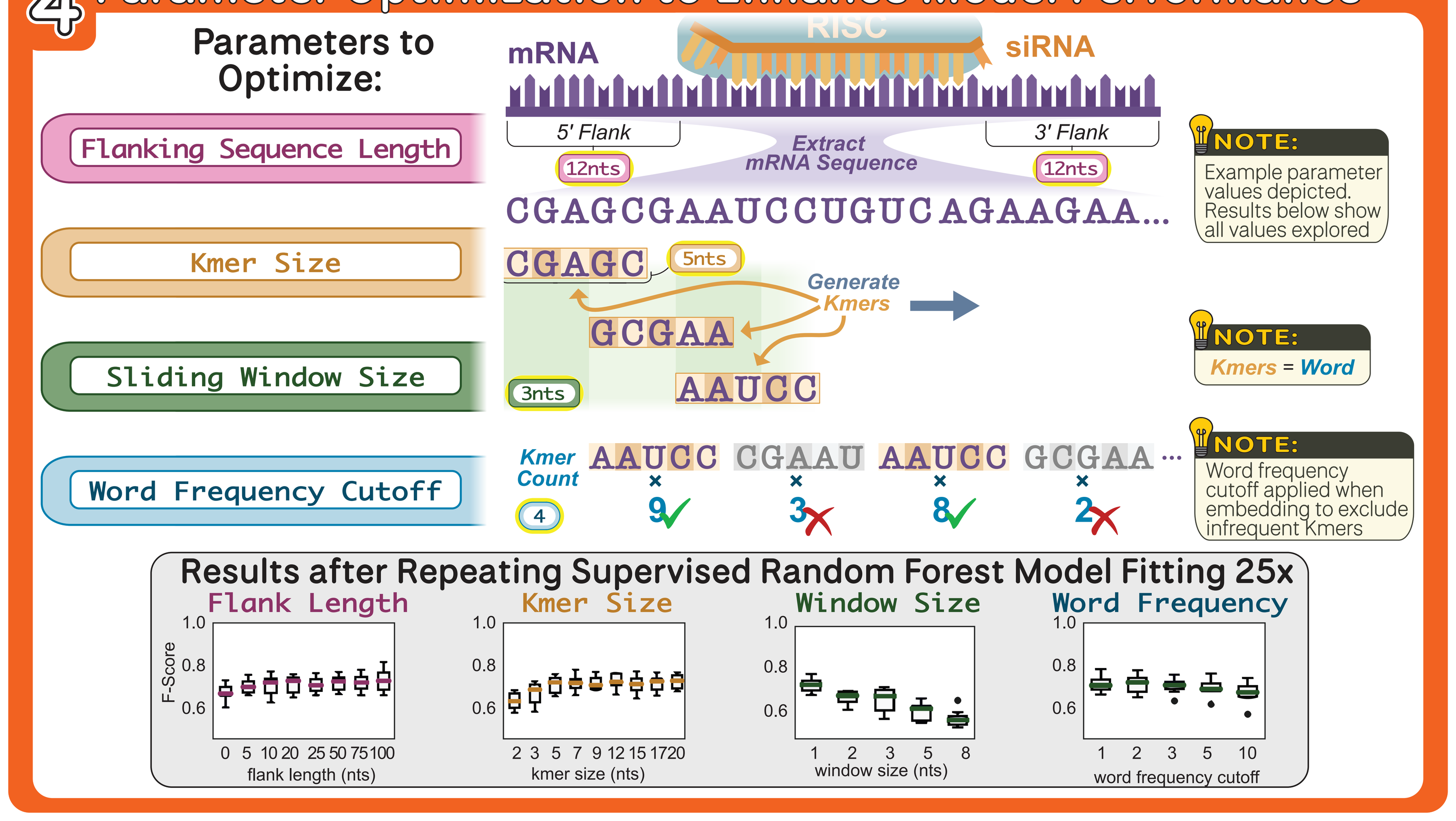
*GloVe applied to semi-supervised models only

Results after 25x Refitting Model

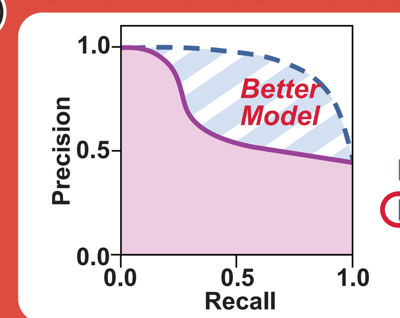


*GloVe applied to semi-supervised models only

4 Parameter Optimization to Enhance Model Performance



5 Performance Evaluation Metrics: Precision-Recall Curve & F-Score



$$\text{Precision} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}}$$

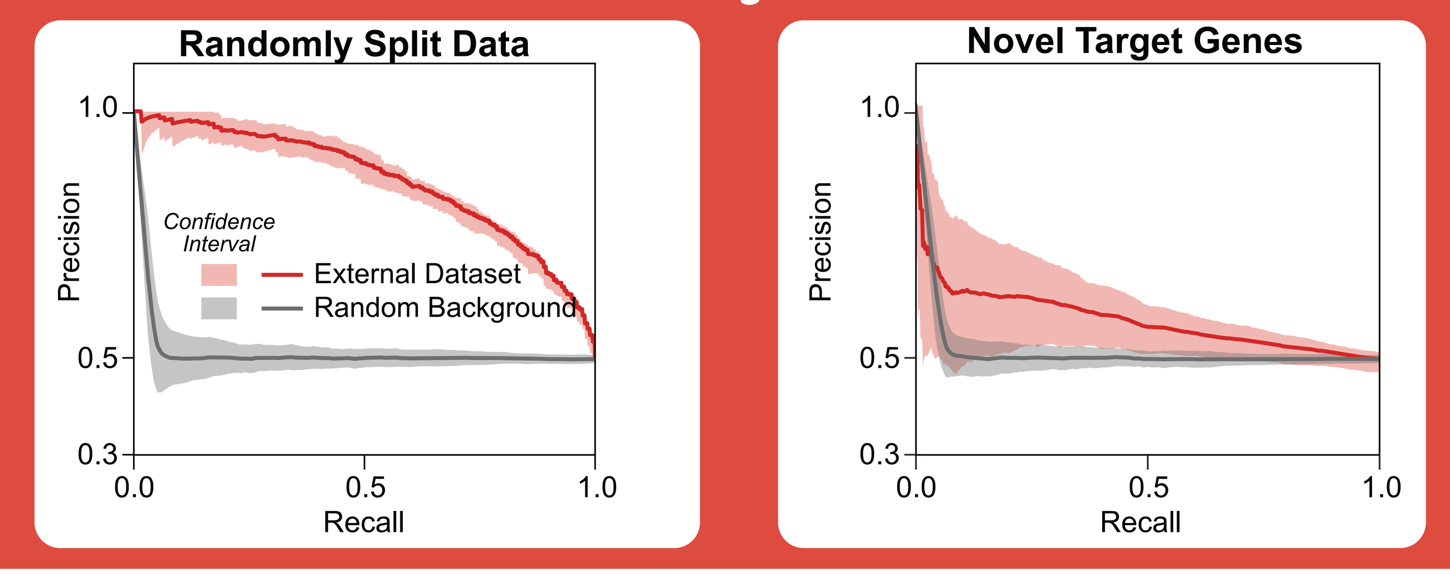
$$\text{Recall} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$

$$\text{F-Score} = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}}$$

F-Score combines Precision and Recall into a single metric

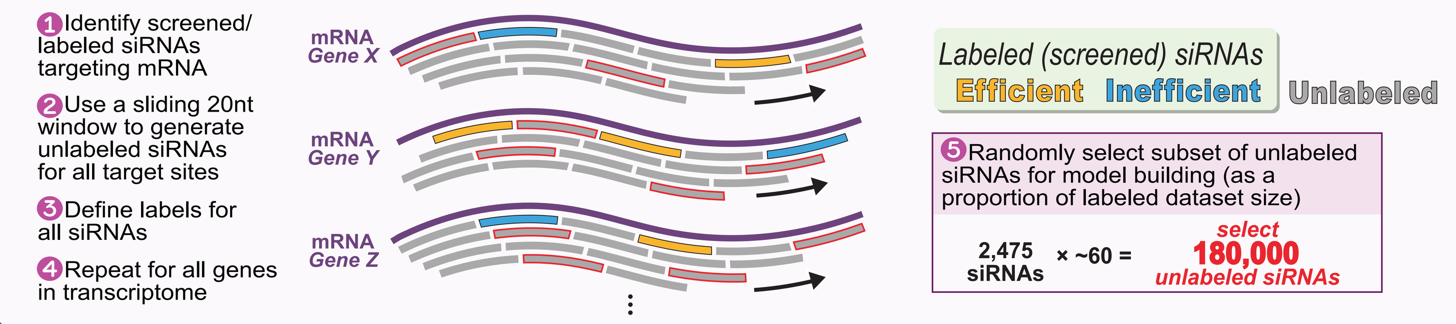
Useful for quick assessments (model optimization)

Supervised Model is Highly Predictive on Randomly-Split Data but not Novel Target Genes

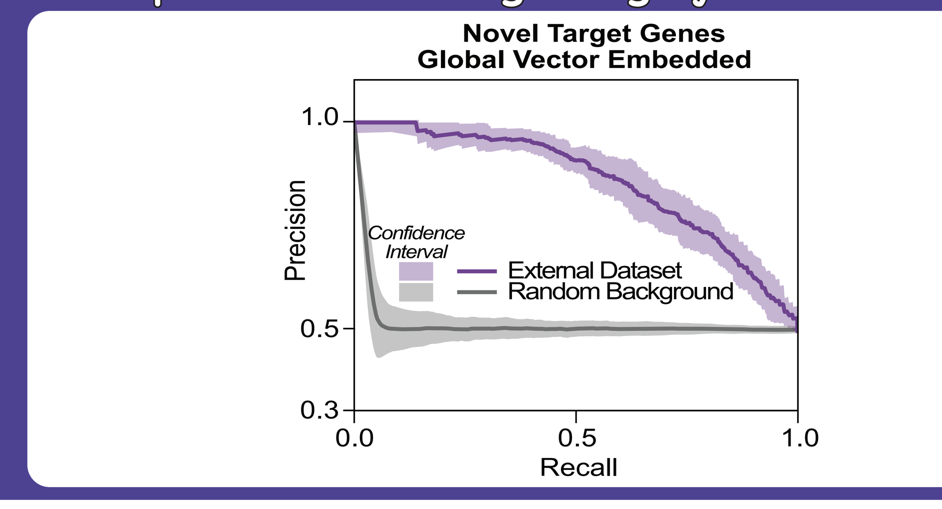


6 Semi-Supervised Learning Applies Unlabeled Data

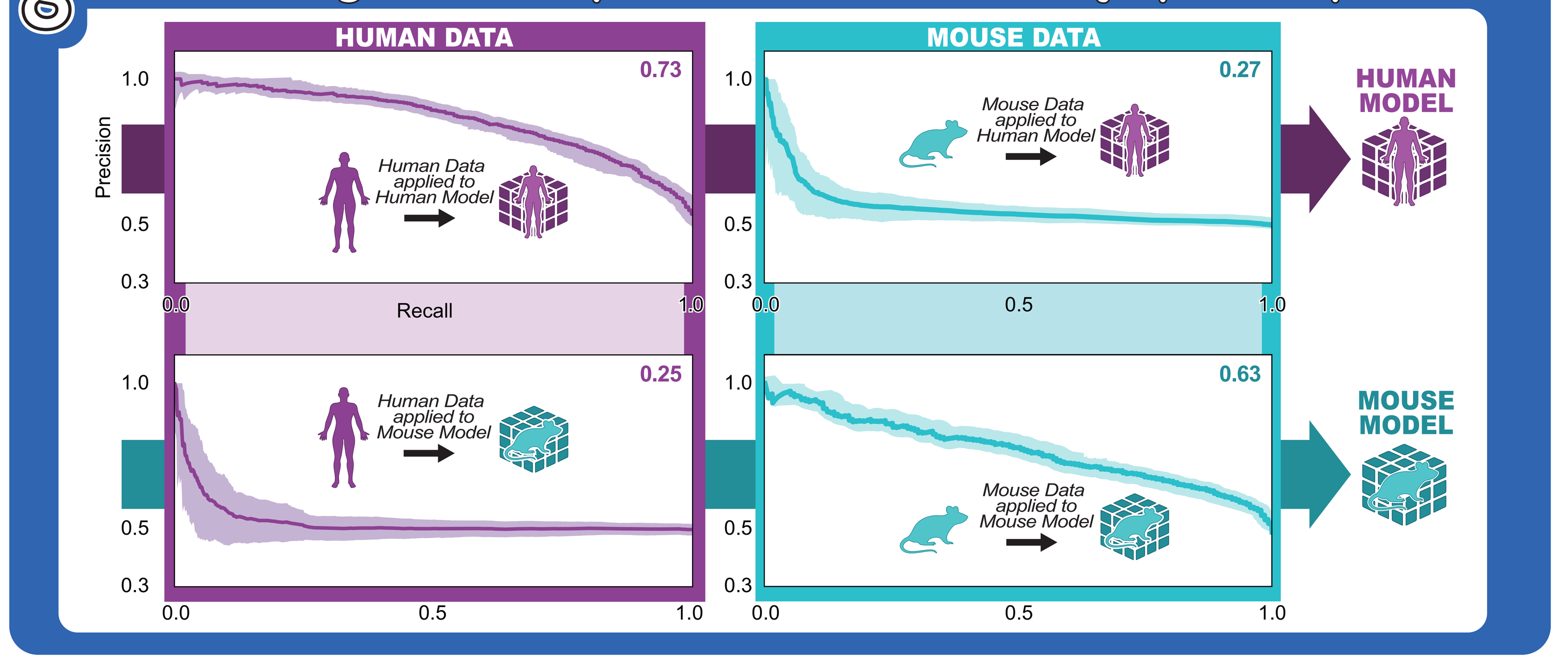
Generating Unlabeled Data: siRNAs with Unknown Efficacies



7 Semi-Supervised Learning is Highly Predictive on Novel Targets

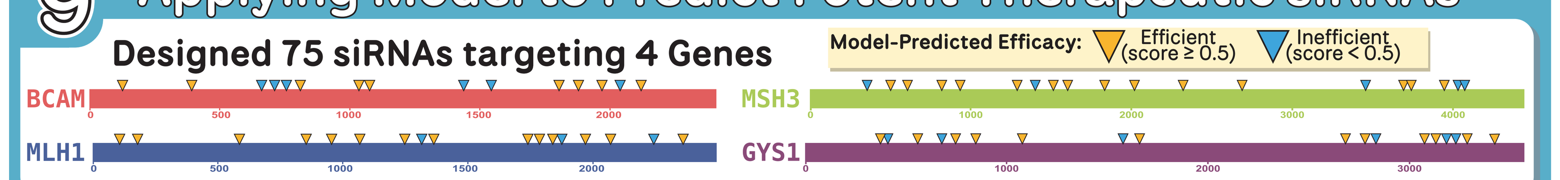


8 siRNA Design: Semi-Supervised Model is Strictly Species Specific



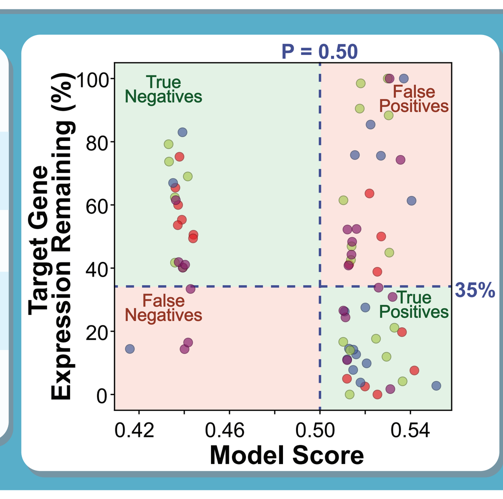
9 Applying Model to Predict Potent Therapeutic siRNAs

Designed 75 siRNAs targeting 4 Genes



Experimentally Validating siRNA Efficacy Prediction Model

1. Apply model to score siRNAs targeting 4 new genes not in dataset
2. Select top 15-18 scoring and 3-6 bottom-scoring compounds per gene
3. Synthesize 75 siRNAs in fully modified therapeutically permissive scaffold*
4. Evaluate endogenous target transcript knockdown in human HeLa cells



Semi-Supervised Model

	Inefficient (Predicted)	Efficient (Predicted)
Inefficient (Actual)	True Negatives 19	False Positives 22
Efficient (Actual)	False Negatives 5	True Positives 29

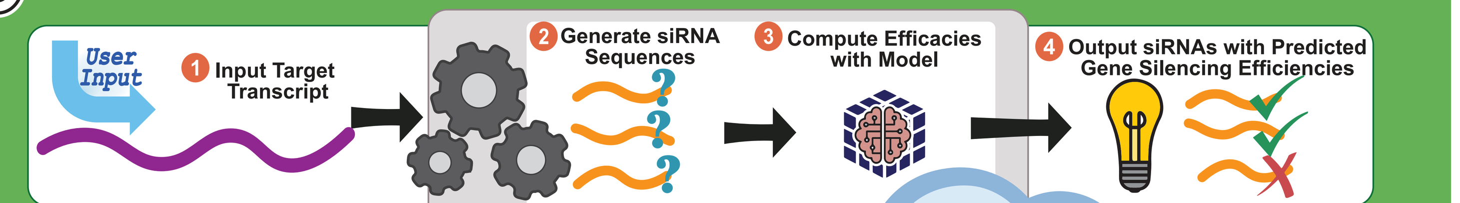
F-Score = 0.73
Accuracy = 64%

Linear Model[2]

	23	28
	11	13

F-Score = 0.40
Accuracy = 48%

10 Algorithm to Design Therapeutic siRNAs is Live!



Scan QR Code To Access Web Application

Questions?
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References

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