Predicting Exon Criticality from Primary Protein Structure

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The Problem: Current models do not predict whether an exon is essential or not (exon criticality)

Can a pre-mRNA exon be alternatively spliced?
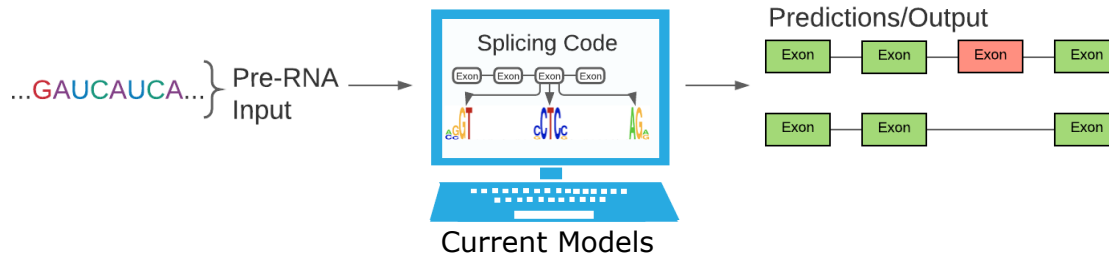
Current Models

Is an exon critical to the protein?
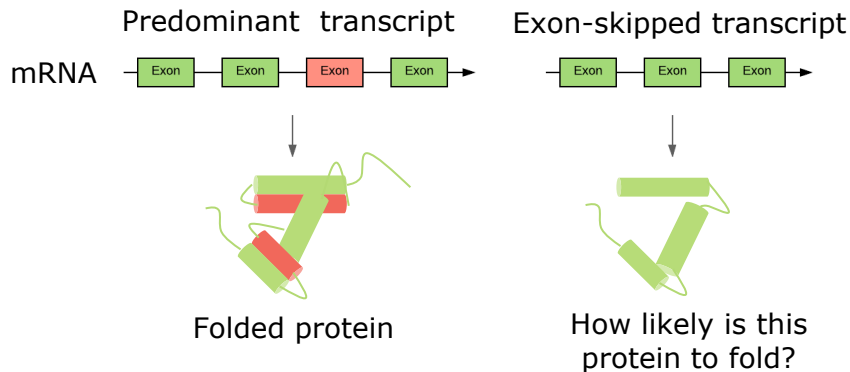
# Exon ByPASS learns exon criticality from nature

Current models do not predict whether an exon is essential or not (exon criticality)

Does the skipped sequence make sense?

Genetic medicines bring great hope to patients

Genetic medicines bring hope to patients → Yes

~~Genetic~~ great hope to patients → No

Medicines bring great hope to patients → Yes

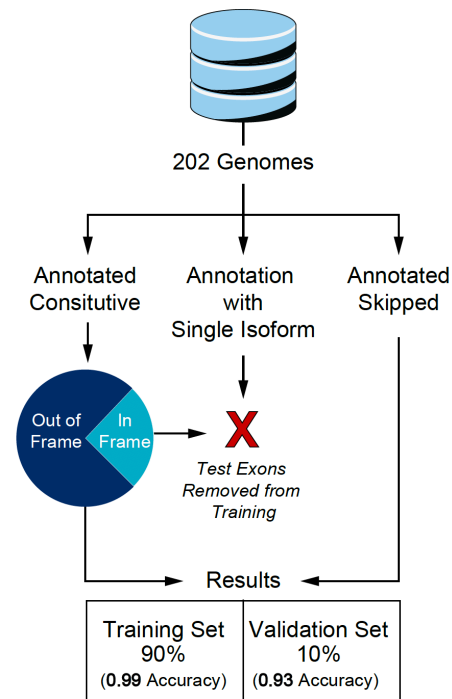### Deep learning models can use sequence context to help identify necessary exons

Exon — Exon — Exon — Exon — Exon
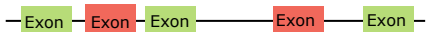
AGHTVH   FHHLPQ   LVMNFR   ASKLERG   KYGHTA

Can proteins from skipped transcripts exist?

AGHTVH LVMNFR ASKLERG KYGHTA → Yes

AGHTVH ~~ASKLERG~~ ~~KYGHTA~~ → No

AGHTVH LVMNFR KYGHTA → Yes

We train the model on millions of known protein sequences

202 Genomes

Annotated Consitutive | Annotation with Single Isoform | Annotated Skipped

Out of Frame | In Frame

Test Exons Removed from Training

Results

| Training Set 90% (**0.99** Accuracy) | Validation Set 10% (**0.93** Accuracy) |

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Exon ByPASS: predicting Exon-skipping Based on Protein Amino acid SequenceS
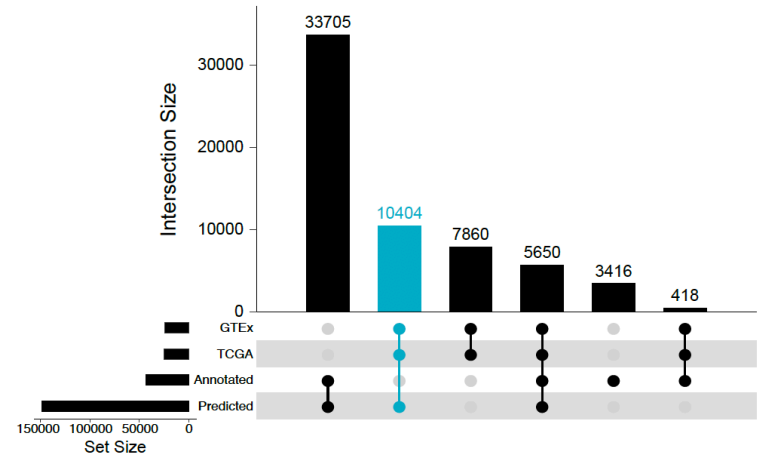
4

Exon ByPASS predicts thousands of skippable exons in the human genome

Exon ByPASS predicts unannotated skippable exons
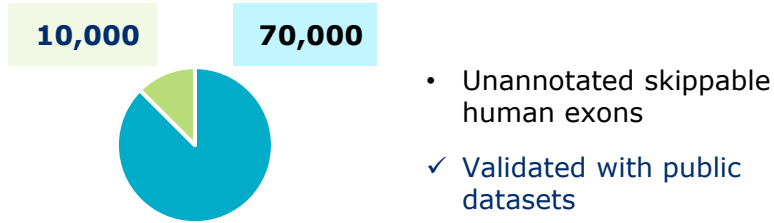
Probability that exons are skippable

Skip Probability
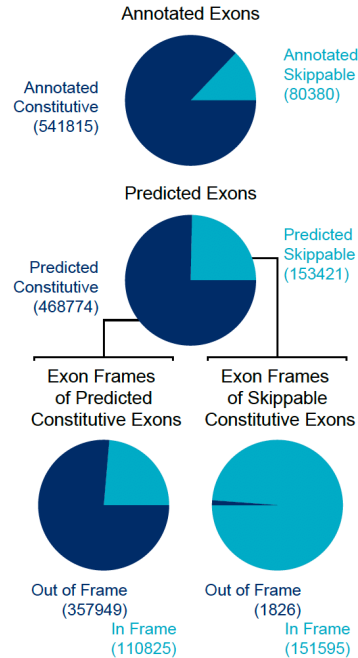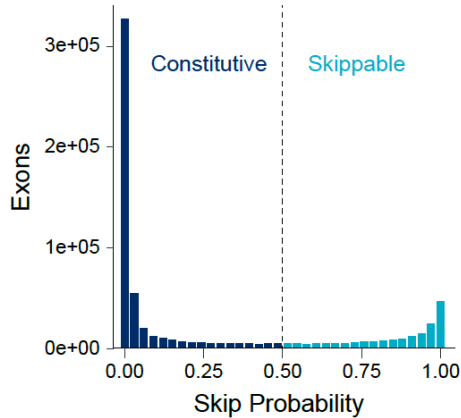
Many predicted skippable but unannotated exons are validated in public data

Annotated Exons

Annotated Skippable (80380)

Annotated Constitutive (541815)

Predicted Exons

Predicted Skippable (153421)

Predicted Constitutive (468774)

Exon Frames of Predicted Constitutive Exons

Exon Frames of Skippable Constitutive Exons

Out of Frame (357949)

In Frame (110825)

Out of Frame (1826)

In Frame (151595)

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Summary

Skippable exons

10,000   **70,000**

- Unannotated skippable human exons
- ✓ Validated with public datasets

Clinically relevant genes with skippable exons

Experimentally confirmed (PubMed)

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~100 genes

Exon ByPASS predicted

2500 genes

Exon ByPASS

- Focus on protein sequence

- Prioritizes skipped exons that yield folded proteins

- May predict therapeutic exon skipping targets

- Predictions are a Wave Discovery resource

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