Scikit-ribo - Accurate A-site prediction and robust modeling of translational control

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AGBT

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CSH Stanley Institute for Cognitive Genomics Cold Spring Harbor Laboratory

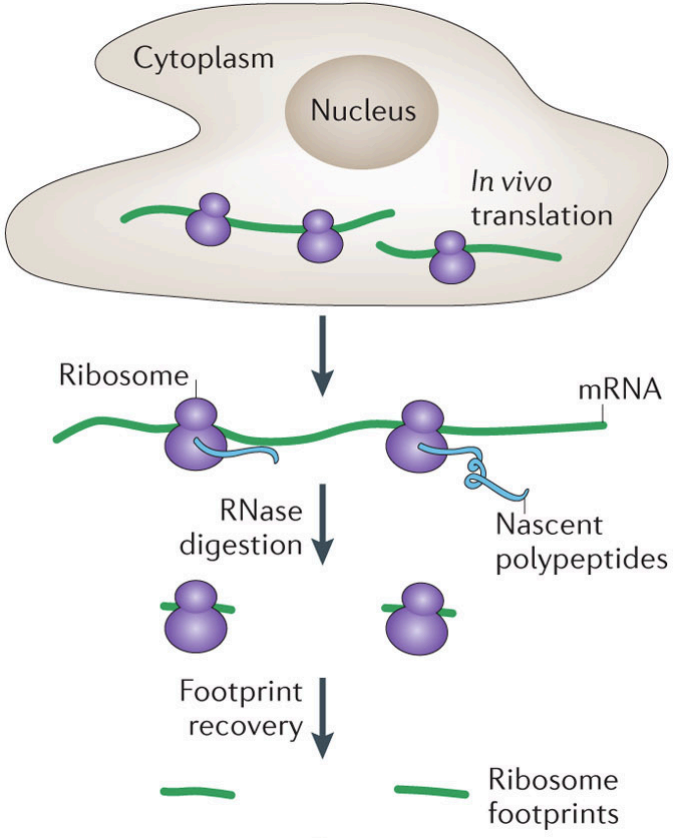
SFARI Simons Foundation Autism Research Initiative

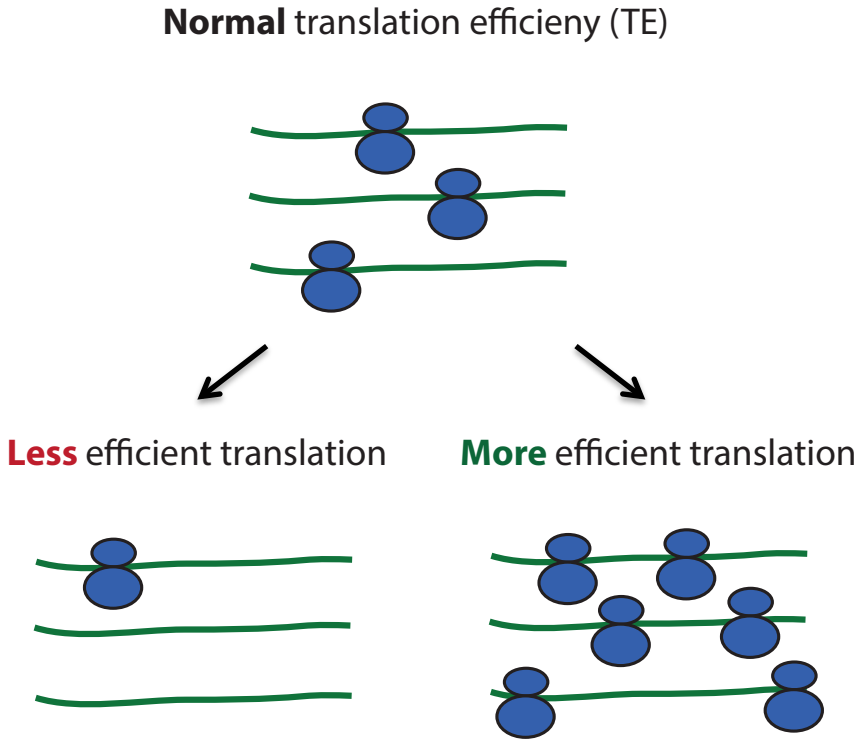
NSF

Stony Brook University

Central dogma of biology – Classic view

What is ribosome profiling (Riboseq)?

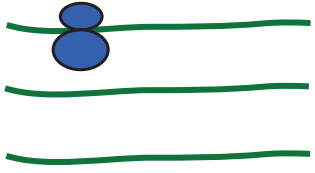




Ingolia. *Science.* (2009)
Ingolia. *Nat Rev Genet.* (2014)

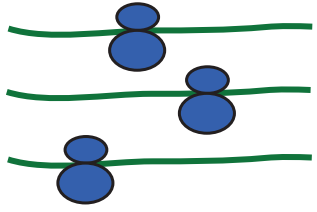
Calculate translational efficiency (TE)

Less efficient translation



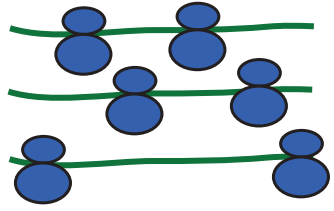
$\log_2(TE) < 0$

Normal translation efficieny (TE)



$\log_2(TE) = 0$

More efficient translation

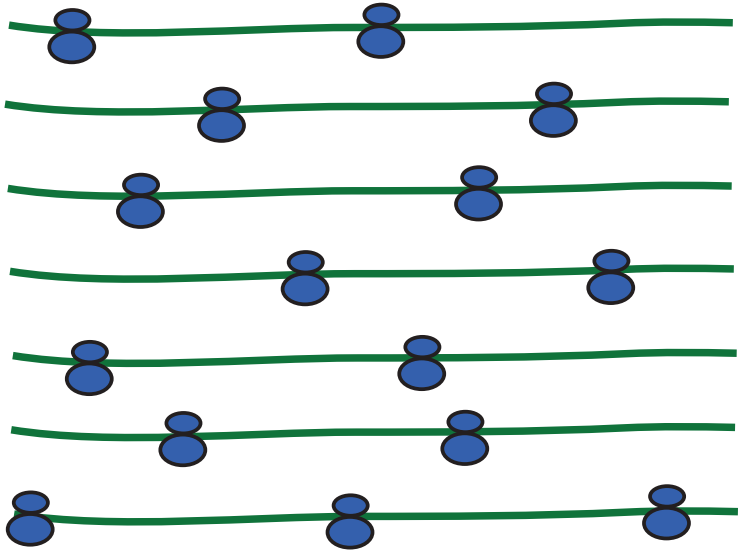


$\log_2(TE) > 0$

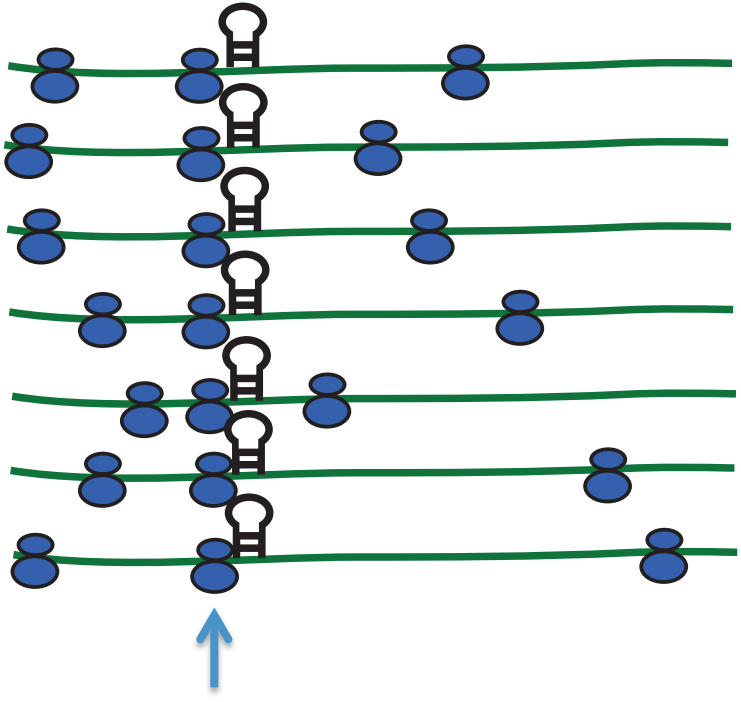
$$TE = \frac{Riboseq\ \ rpkm}{RNAseq\ \ rpkm}$$

Hypothesis: TE distribution could be skewed by ribosome pausing events.

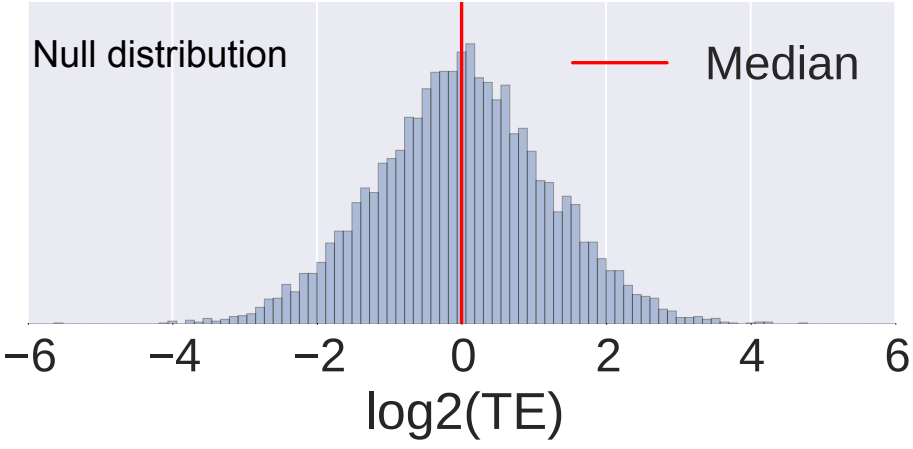
Ribosome footprints without bias

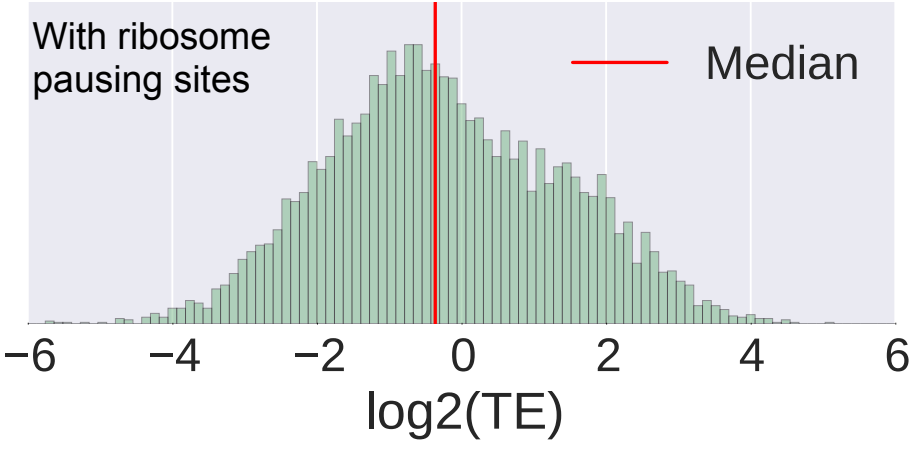


Ribosome footprints with pausing



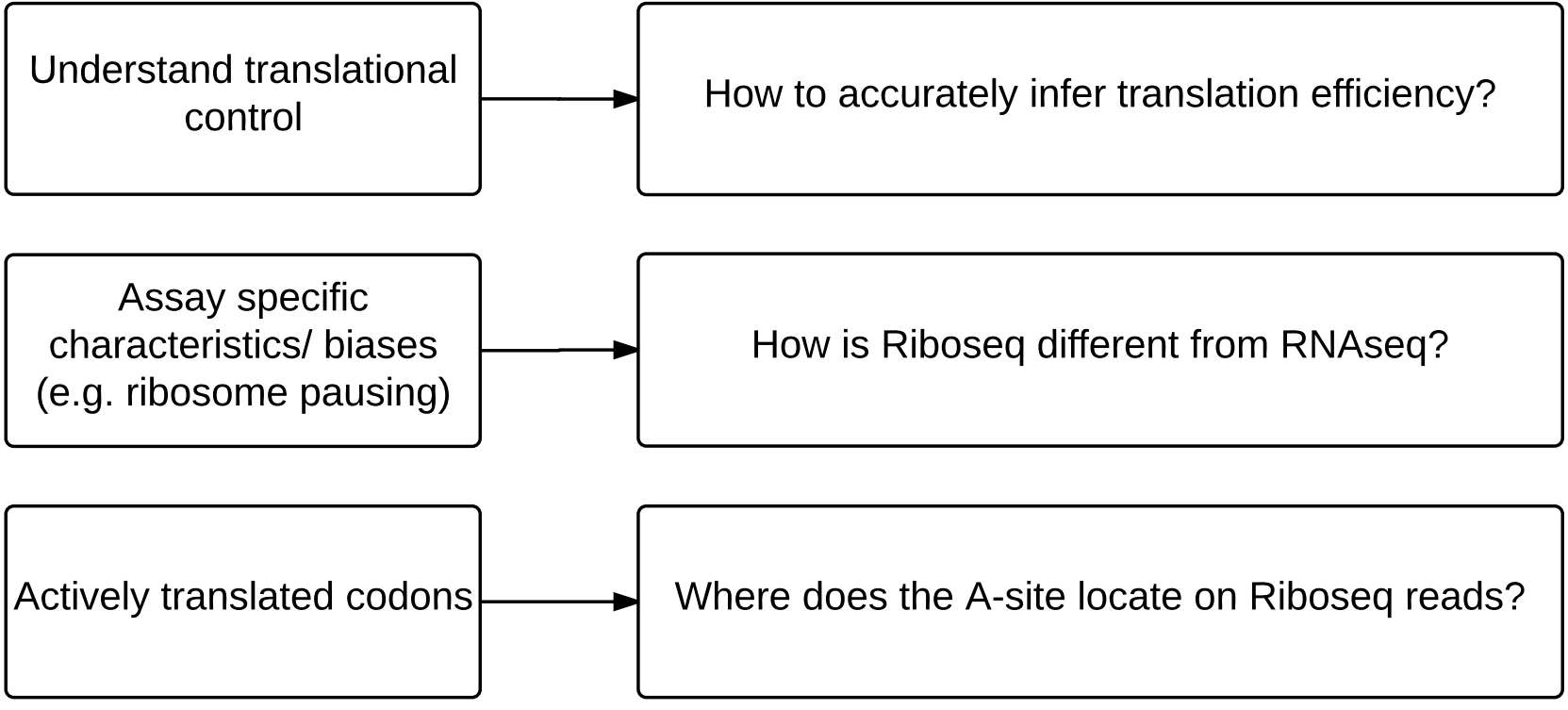
Simulated *S. cerevisiae* data - TE distribution are negatively-skewed by ribosome pausing events



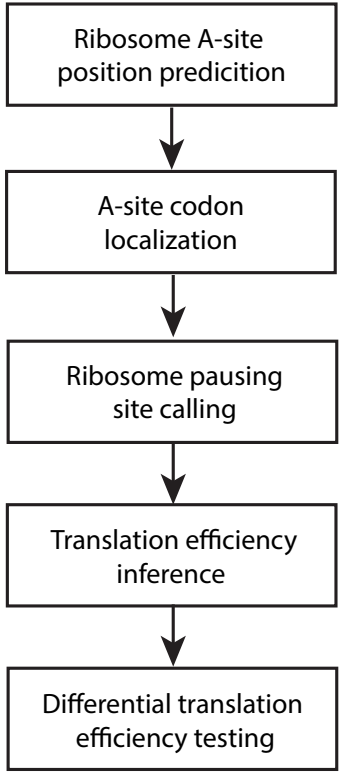


$$TE = \frac{Riboseq\ rpkm}{RNAseq\ rpkm}$$

Analytical Challenges



Introducing scikit-ribo



What and where is the ribosome A-site?

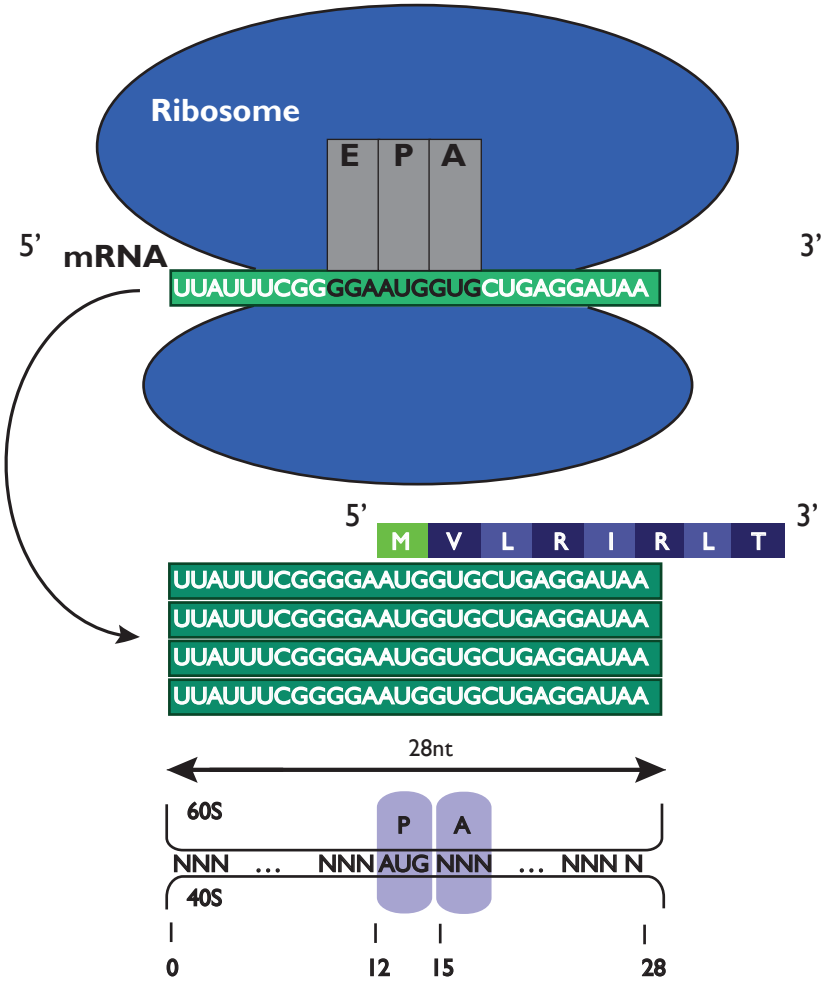
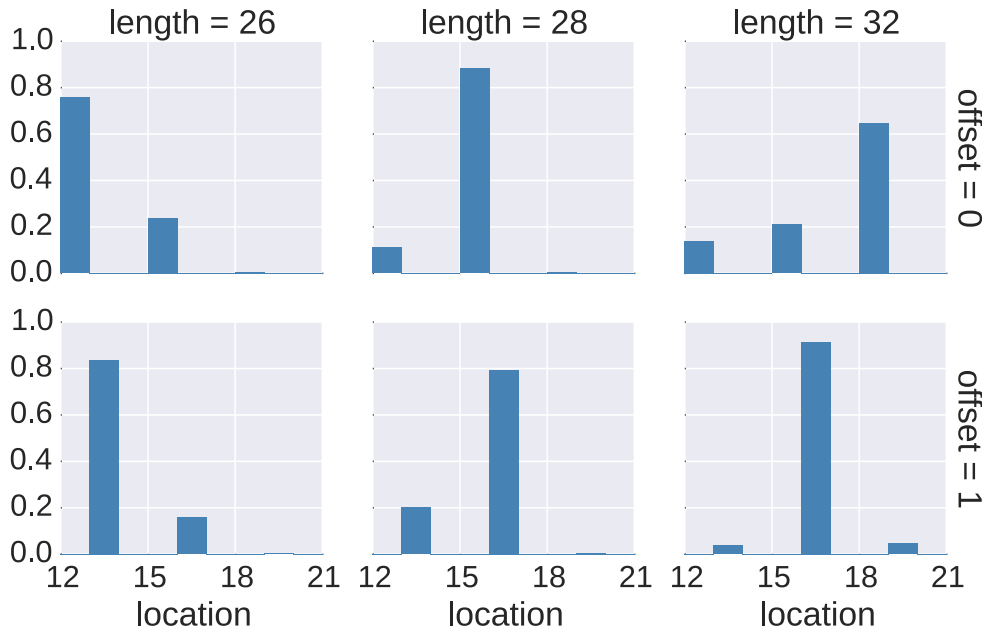
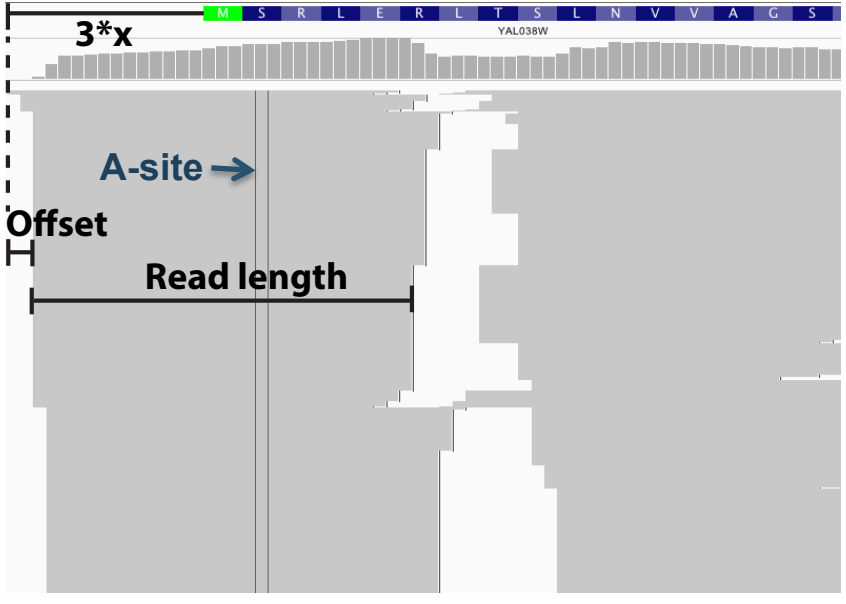


Figure adapted from Ingolia et al. *Science* (2009)



How to predict A-site?

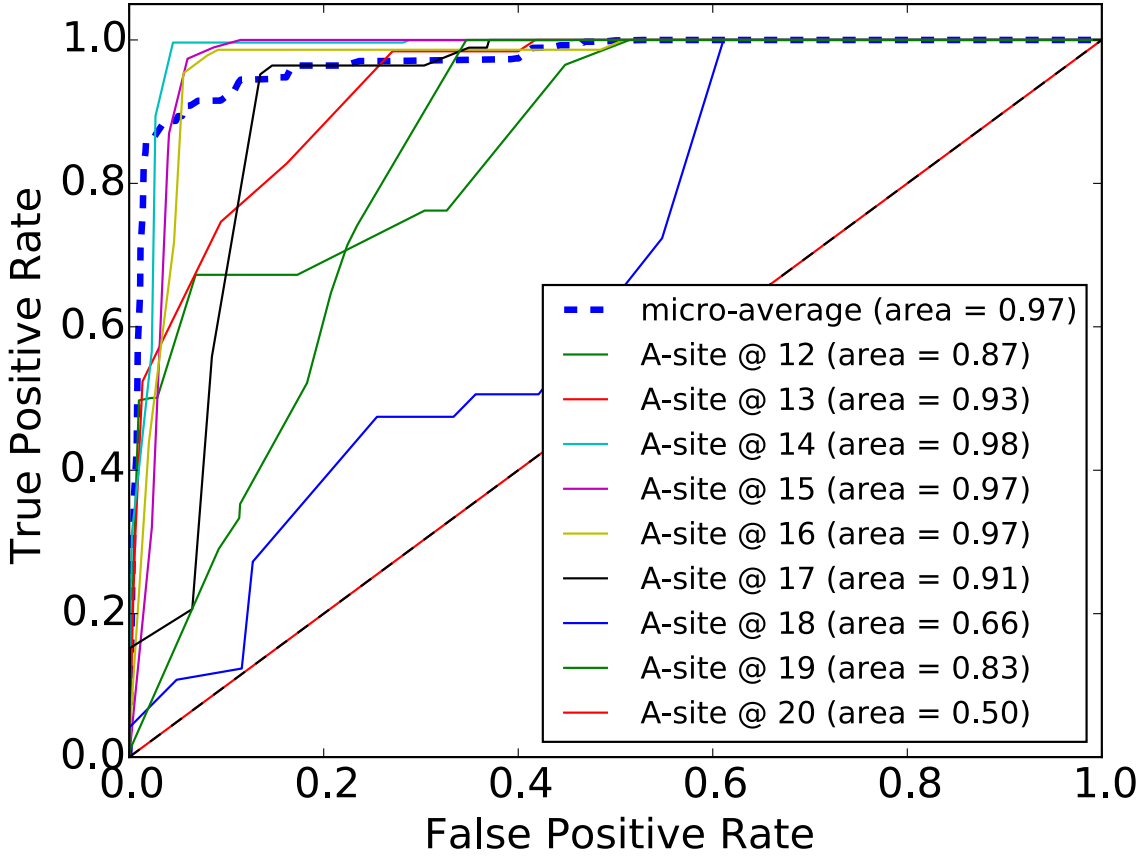
Training data and features:



Classifier and model tuning:

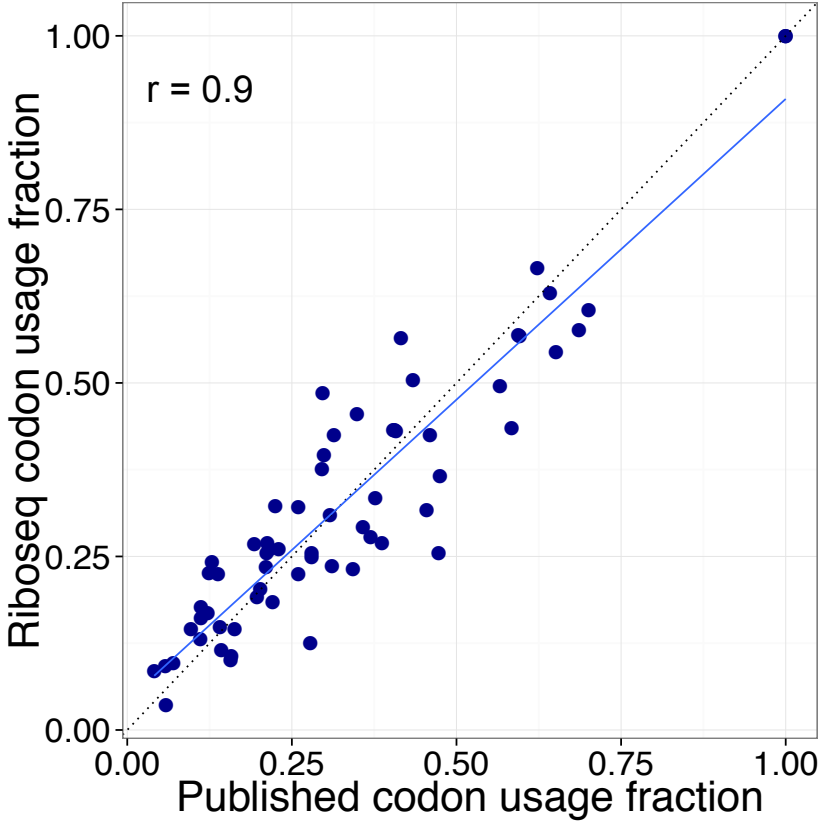
- SVM with RBF kernel (scikit-learn)
- 10 fold cross-validation for grid search
- Make predictions on all reads genome-wide

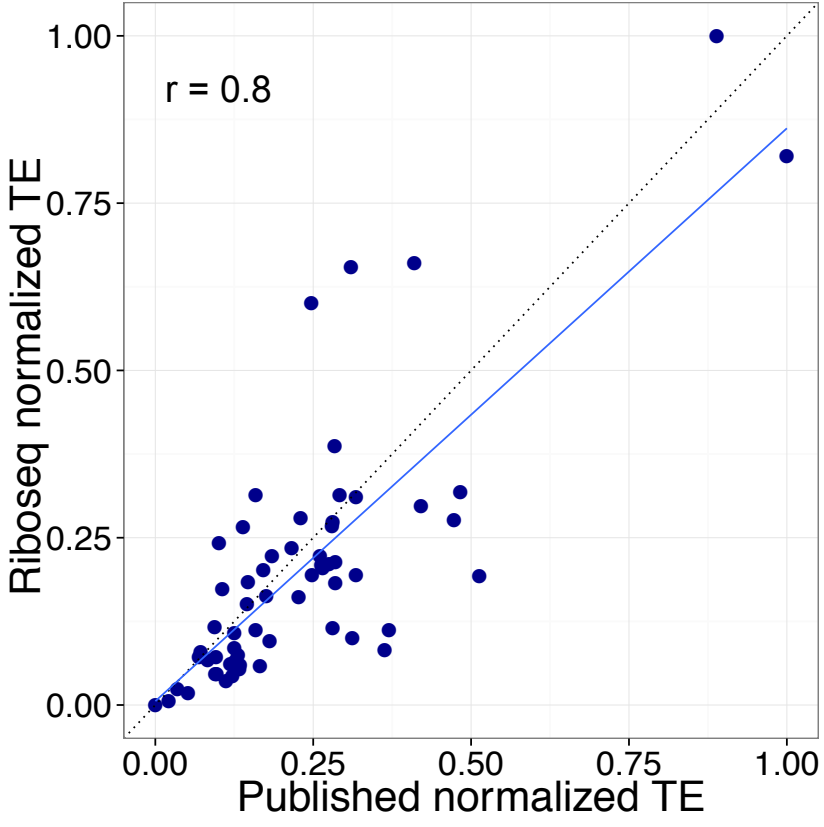
Prediction performance by cross validation



Scikit-ribo has much higher accuracy of identifying A-site than the previous method (0.86 vs. 0.64, 10-fold CV).

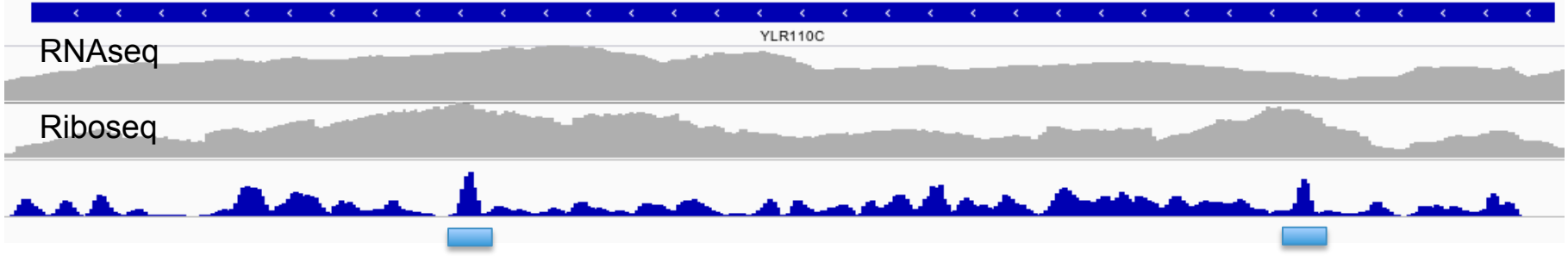
Scikit-ribo accurately predicted codon usage fraction and codon normalized TE





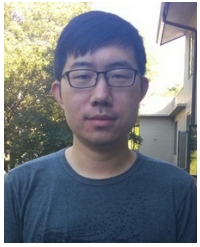
Evolutionary conservation of codon optimality reveals hidden signatures of cotranslational folding, Pechmann, Frydman (2013).

Finding ribosome pausing sites (peaks) is hard. But it is easier after knowing the A-site location.



Q: how to robustly identify ribosome pausing sites while accounting for over-dispersion?

Ribosome pausing site identification by negative binomial mixture model



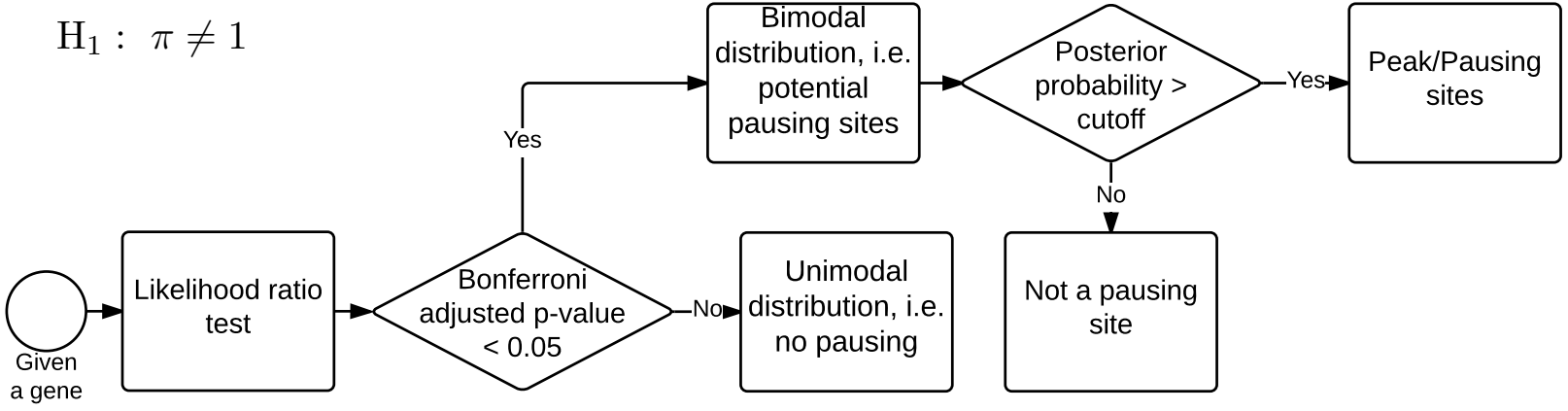
Yifei Huang

$$P(\mathbf{X}_i|\pi_i,\mu_i,k_i,r_i) = \prod_j \pi_i \mathcal{NB}(X_{ij}|\mu_i,r_i) + (1-\pi_i)\mathcal{NB}(X_{ij}|k_i\mu_i,r_i),$$

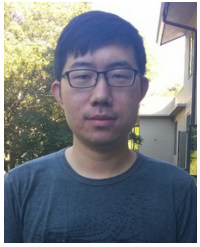
for gene i at position j, where k ≥ 5

$H_0: \ \pi = 1$

$H_1: \ \pi \neq 1$



Ribosome pausing site identification by negative binomial mixture model



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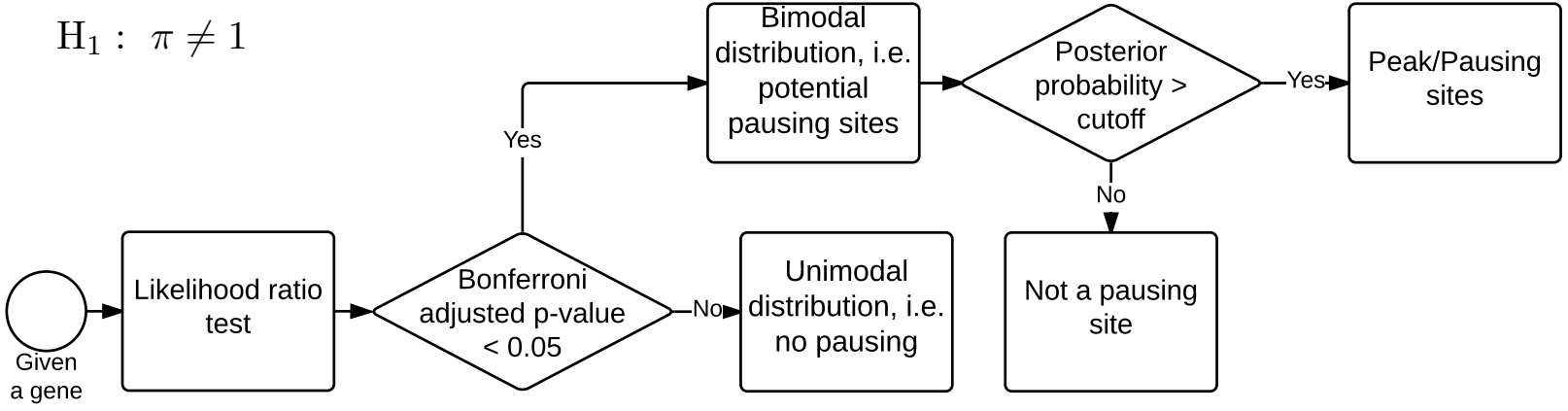
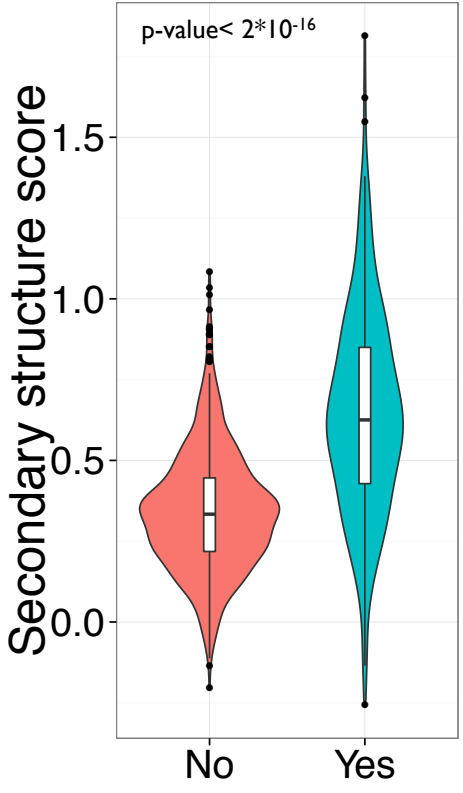
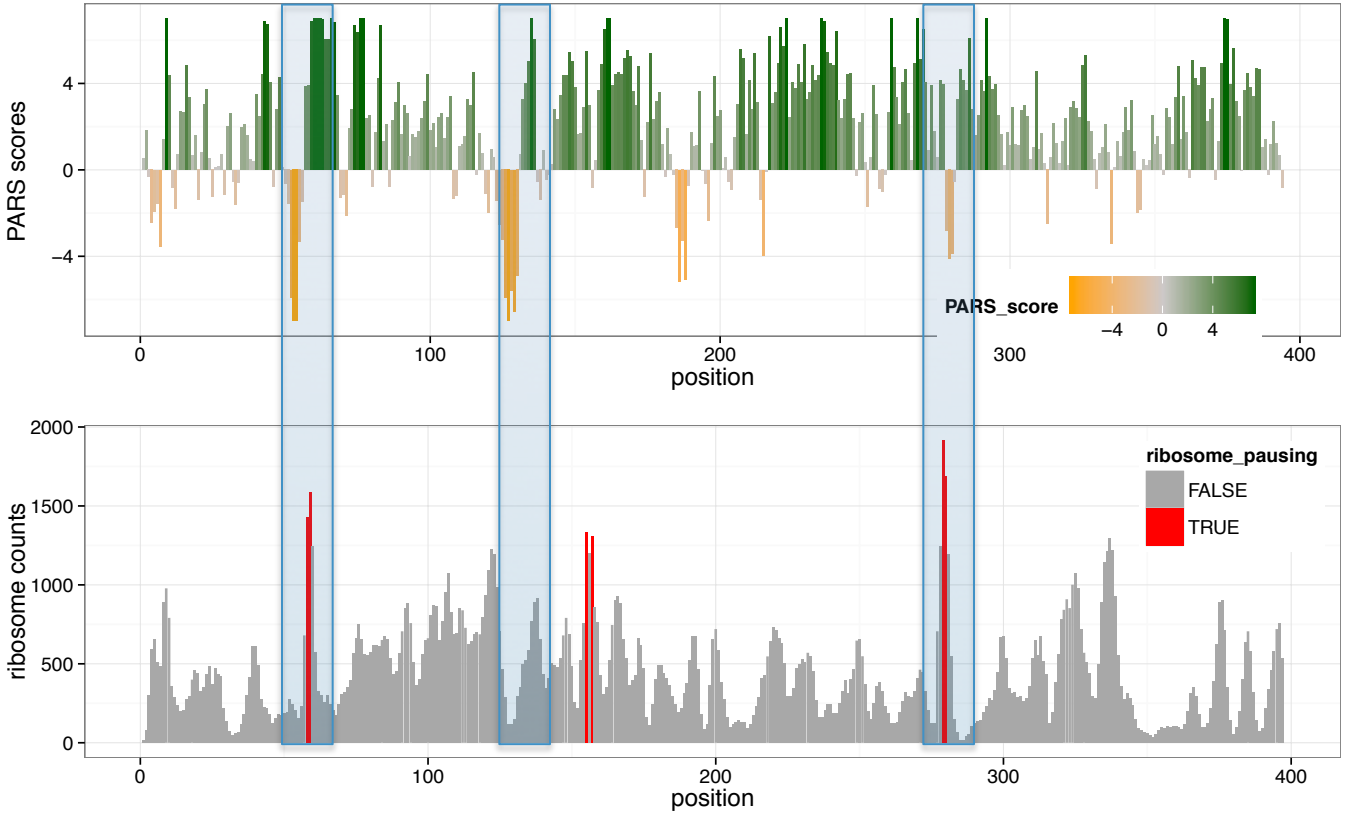


# genes	# genes (rpkm > 100)	# genes with pausing	# ribosome pausing sites identified
6664	1252	94	180

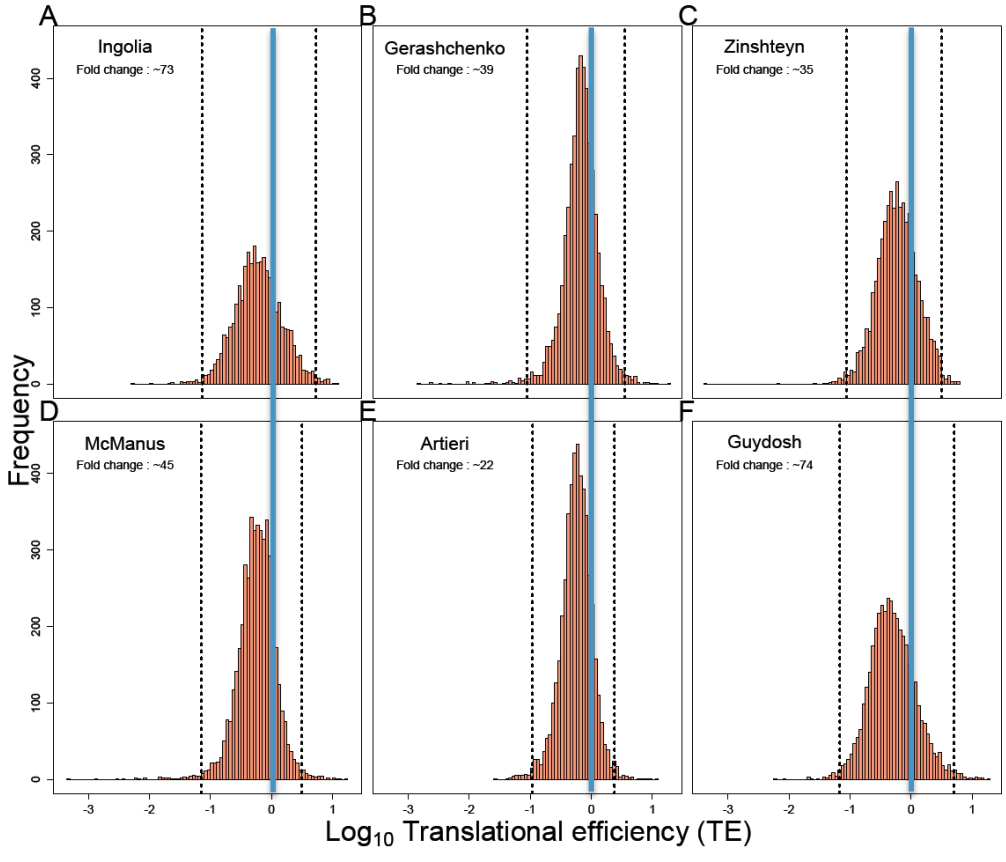
mRNA with stronger secondary structure tend to have ribosome pausing events

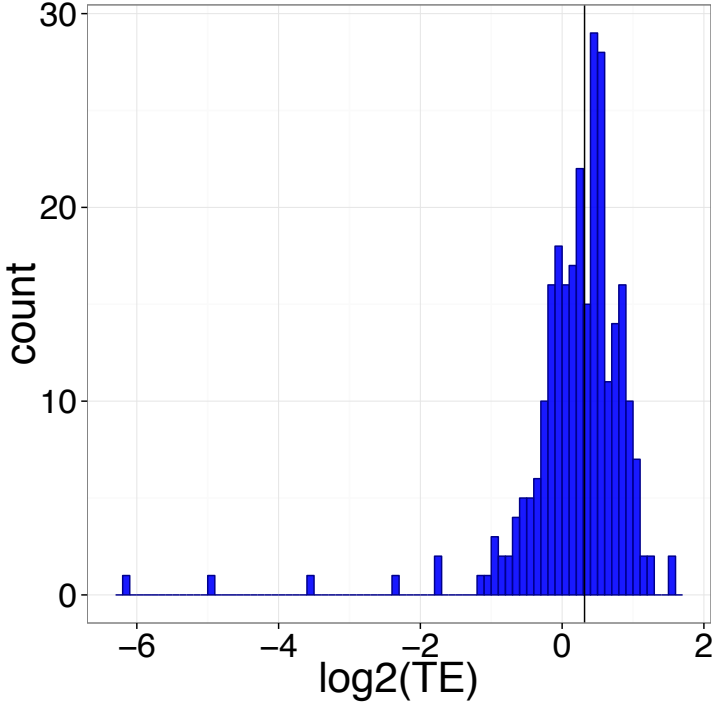




PARS scores obtained from Kertesz et al. Nature (2010)

TE distributions are negatively-skewed in many studies. Over-structured mRNA show inflated TE.





Chi Square test p-value < $2*10^{-16}$

Weinberg, Shah et al. (2015)

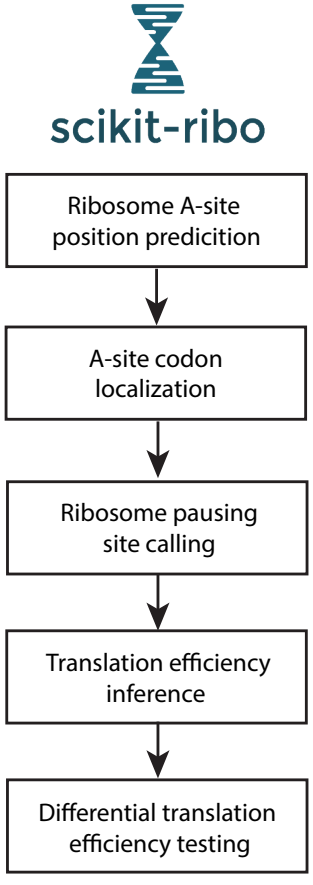
Summary

Discussed:

1) Introduce scikit-ribo for joint analysis of Riboseq & RNAseq data.
2) Learn from data itself to determine ribosome A-site location.
3) Reveal biases in Riboseq data due to ribosome pausing.
4) How Riboseq biases lead to issues with estimating TE.

Ongoing work:

1) Joint inference of codon elongation rates and protein TE.
2) Extend the ribosome pausing calling to a HMM based method.



https://github.com/hanfang/