Quantitating translational control:

mRNA abundance-dependent and independent contributions
and
the mRNA sequences that specify them

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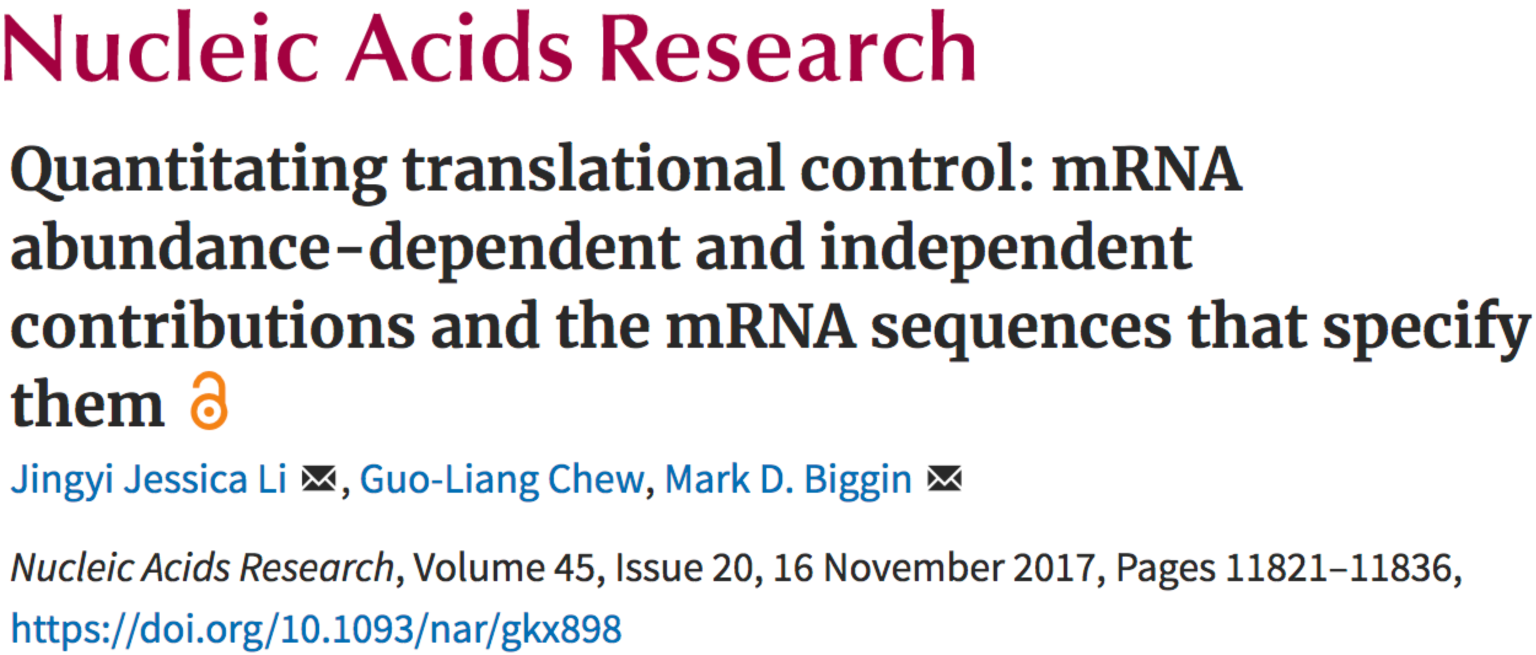

Nucleic Acids Research

Quantitating translational control: mRNA abundance-dependent and independent contributions and the mRNA sequences that specify them

Jingyi Jessica Li ✉, Guo-Liang Chew, Mark D. Biggin ✉

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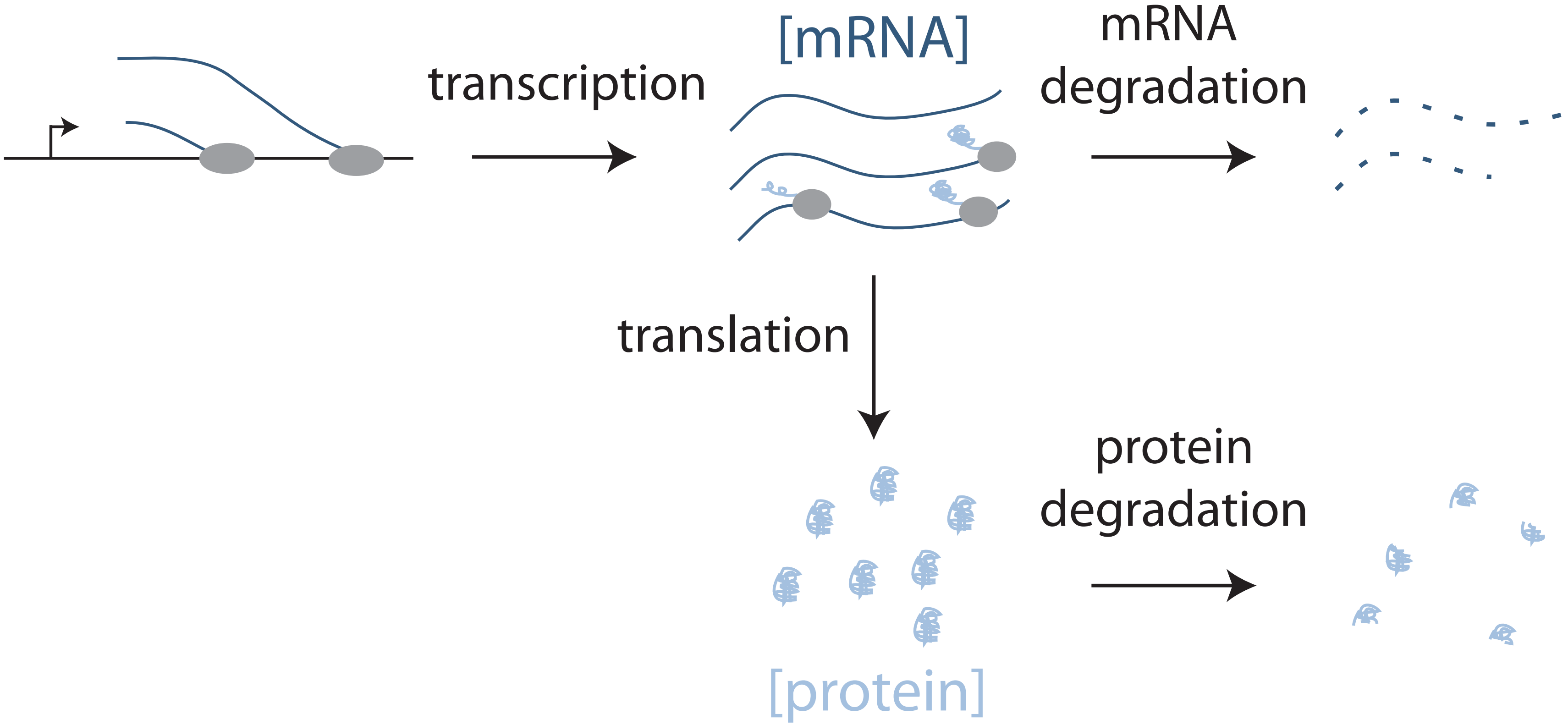
Fred Hutchinson Cancer Research Center

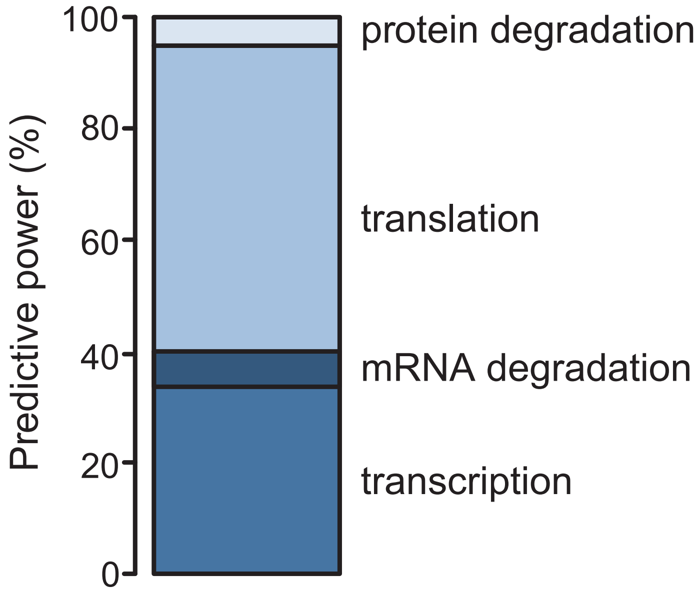
Mark Biggin

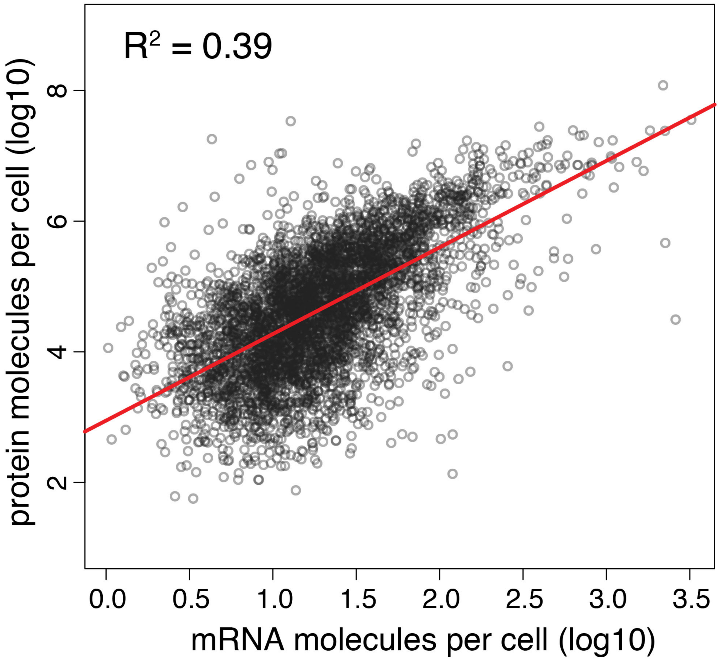
Lawrence Berkeley National Laboratory

Which steps are most important in determining protein levels in animals?



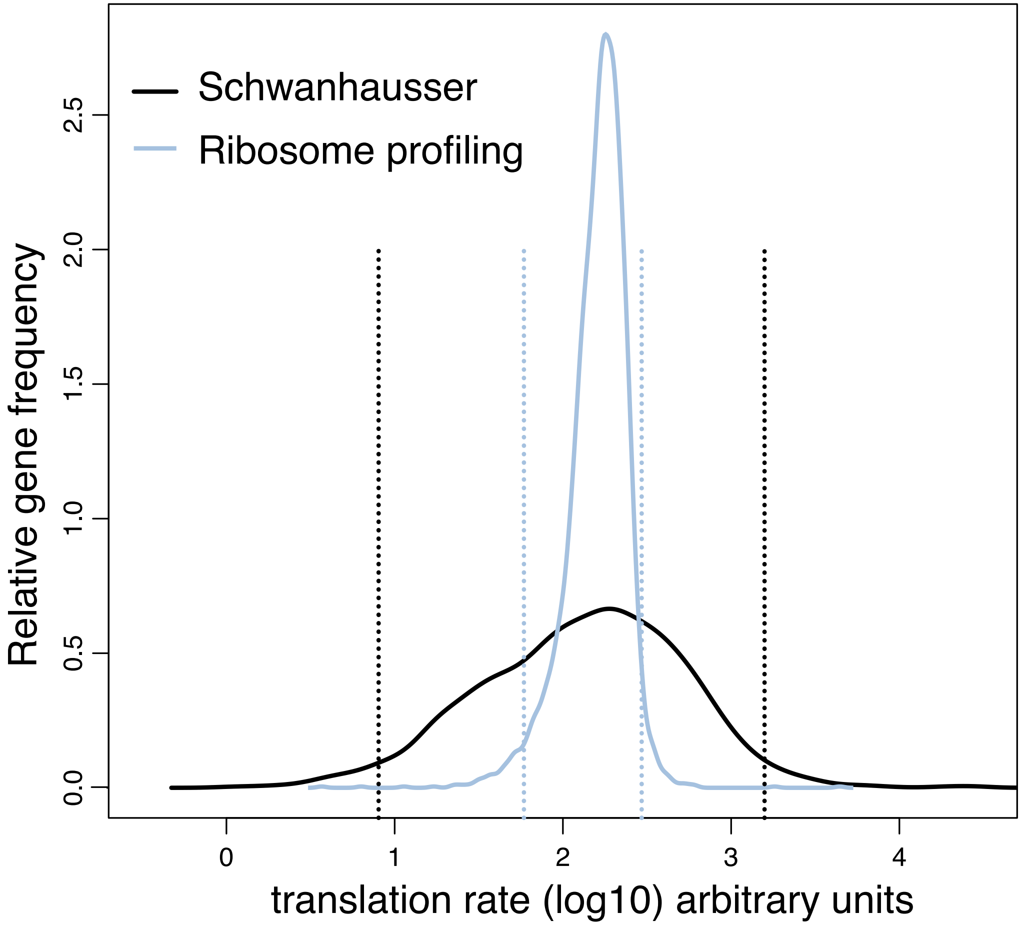
Schwanhausser et al. suggest that translation rates are the most important




measured protein vs measured mRNA

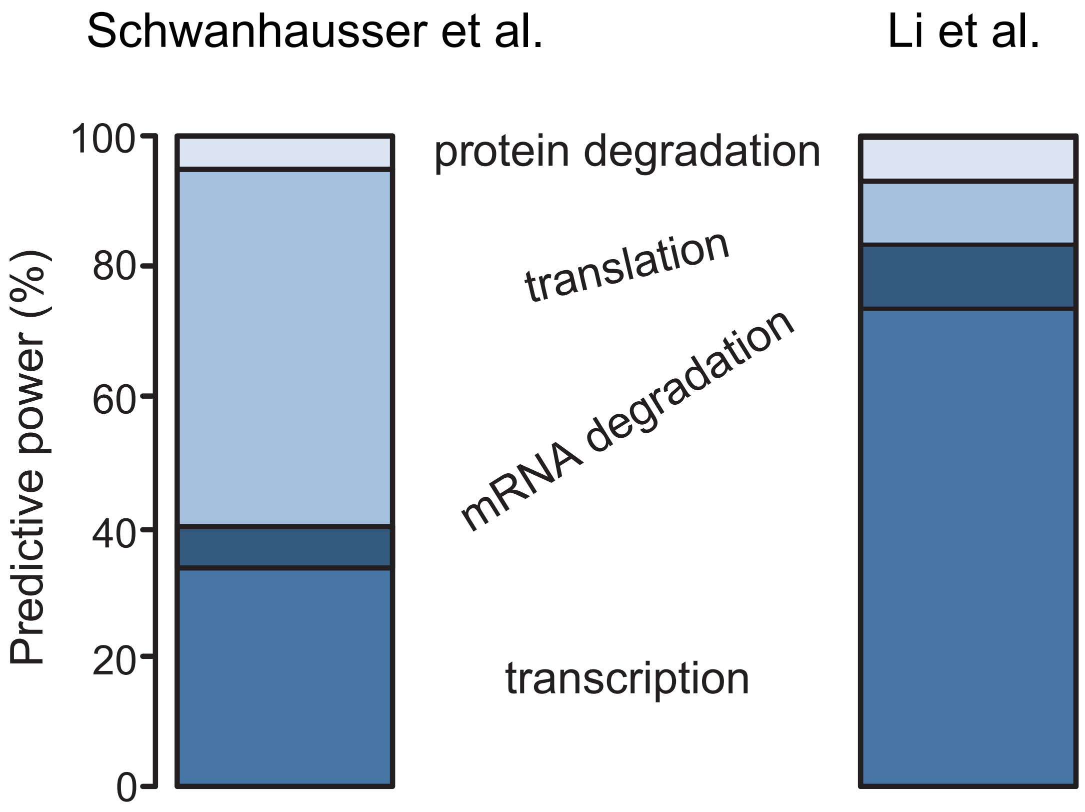
Schwanhausser et al. (2011) Nature 473, p 337

The variance in measured translation rates is 11 fold less than Schwanhausser inferred



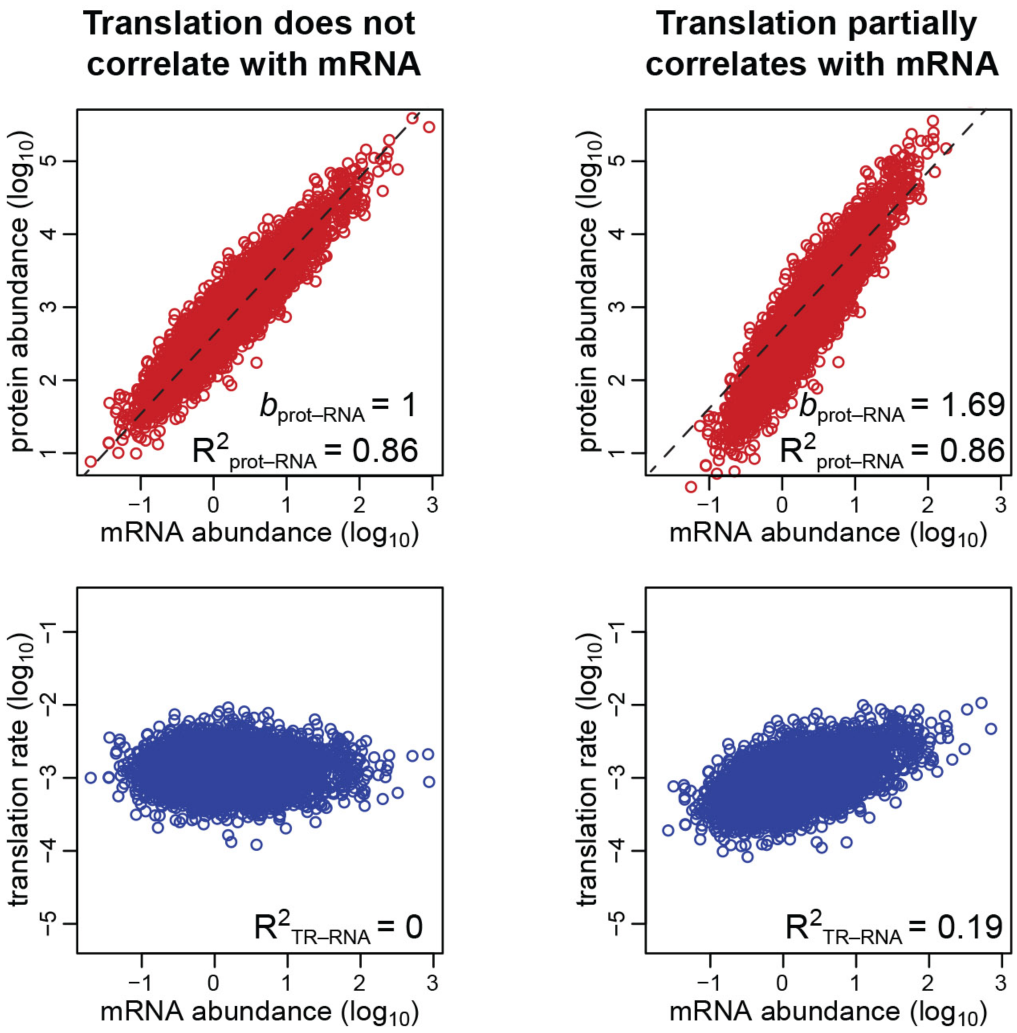
Li et al. (2014) PeerJ: e270.

Transcription is the dominant step determining protein levels



Li et al. (2014) PeerJ: e270; Li and Biggin (2015) Science 347, 1066-1067.

Translation rates impact protein levels in two ways



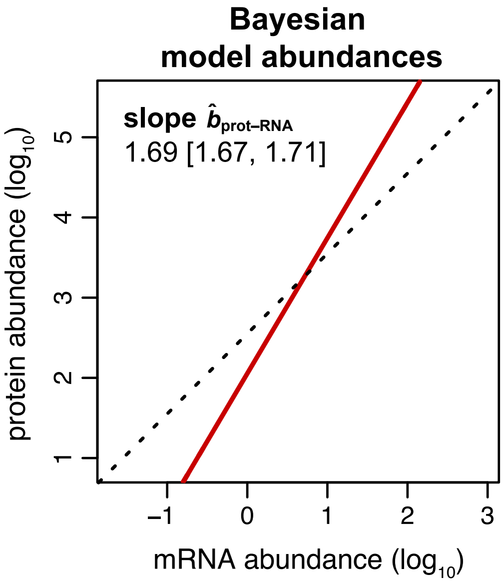
Translation does not correlate with mRNA

Translation partially correlates with mRNA

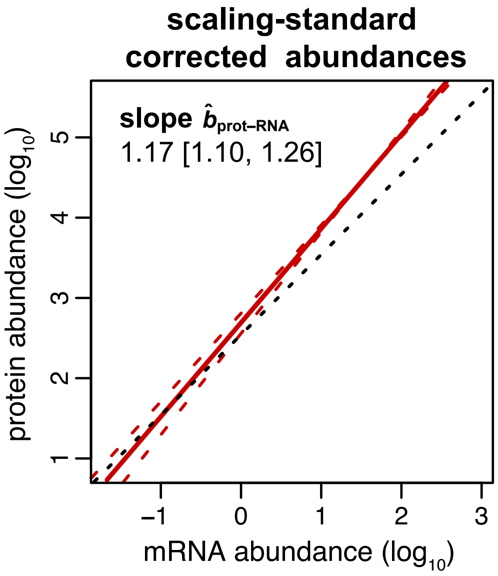
Csardi et al, 2015

Two separate approaches both imply a shallower slope for protein vs mRNA

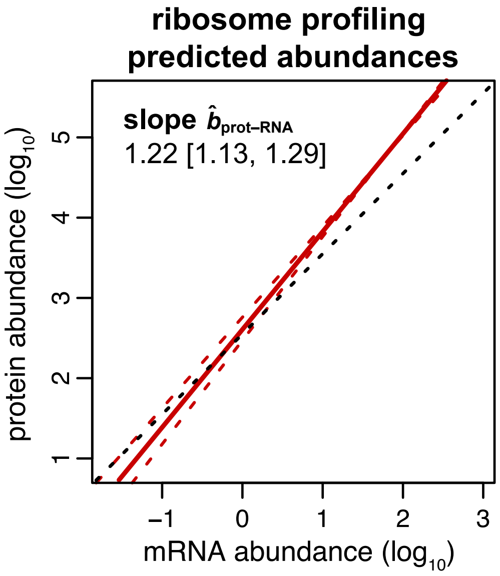
Csardi et al.



Li et al.
Approach 1

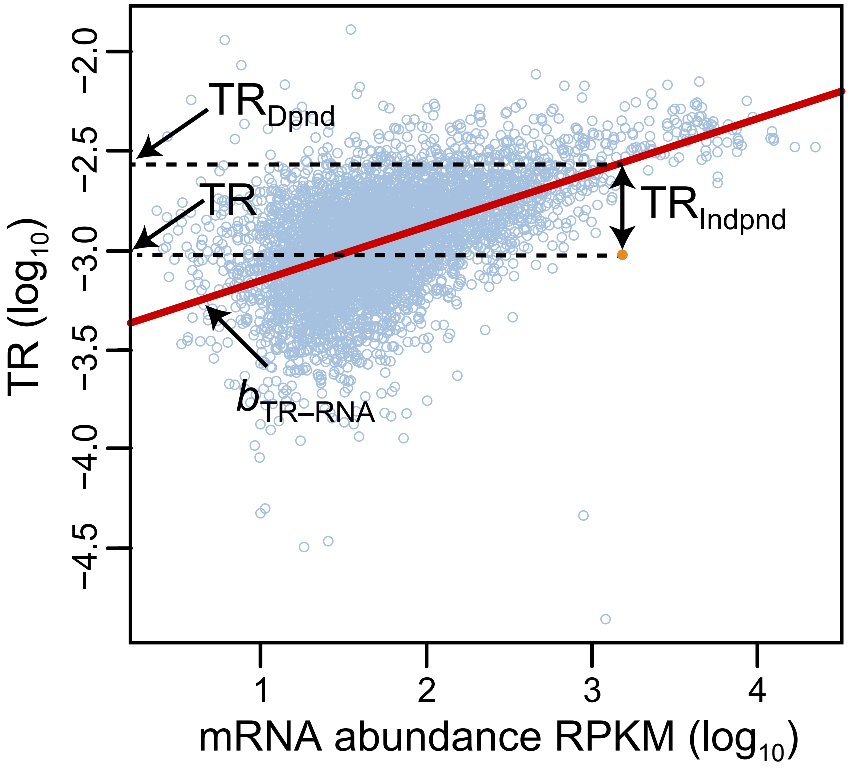


Li et al.
Approach 2



Li et al. (2017) NAR gkx898.

Decomposing TR into two components: TR_{Dpnd} and TR_{Indpnd}



1. Decompose TR

$$\log_{10}(TR_i) = \log_{10}(TR_{Dpnd\,i}) + \log_{10}(TR_{Indpnd\,i})$$

2. Determine slope $b_{TR\text{–}mRNA}$

$$b_{TR\text{-}RNA} = sd(\log_{10}(TR_{Dpnd})) \,/\, sd(\log_{10}(RNA))$$

3. Determine $b_{prot\text{–}mRNA}$ from $b_{TR\text{–}mRNA}$

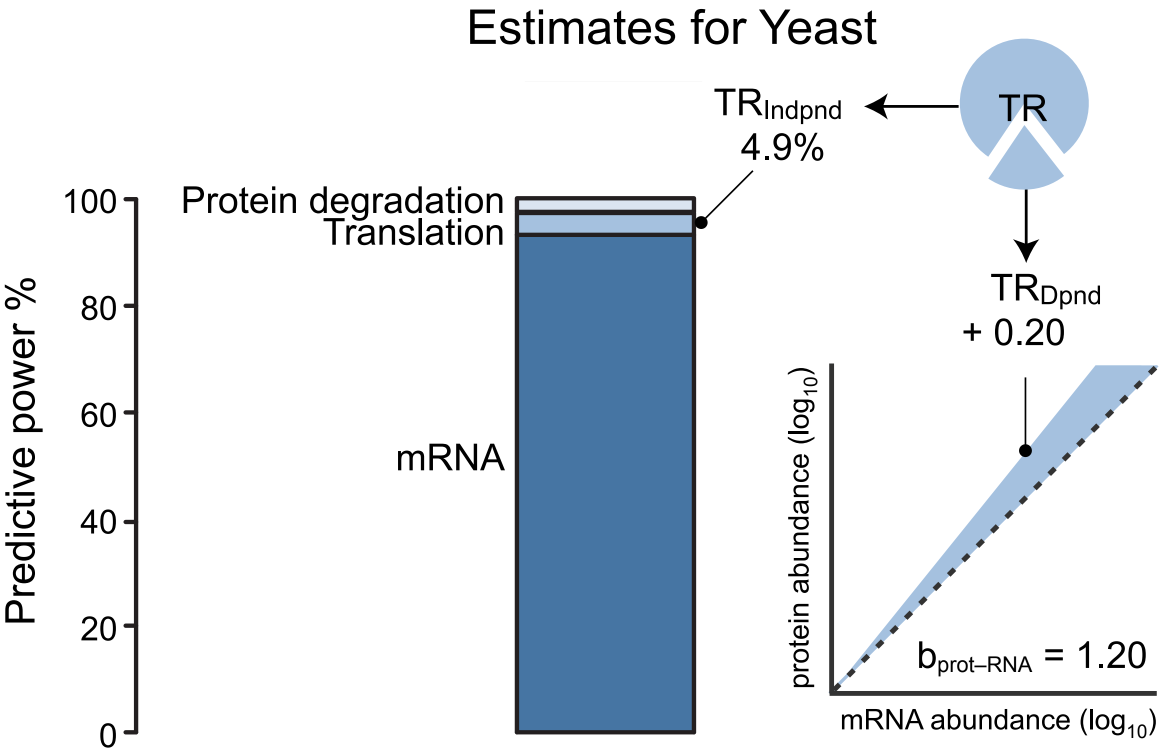
$$b_{prot\text{–}RNA} = 1 + b_{TR\text{–}RNA}$$

4. Define protein via $b_{prot\text{–}mRNA}$ and TR_{Indpnd}

$$\log_{10}(prot_i) = \log_{10}(a) + b_{prot\text{–}RNA}\log_{10}(RNA_i) + \log_{10}(TR_{Indpnd\,i}) + \log_{10}(PnD_i)$$

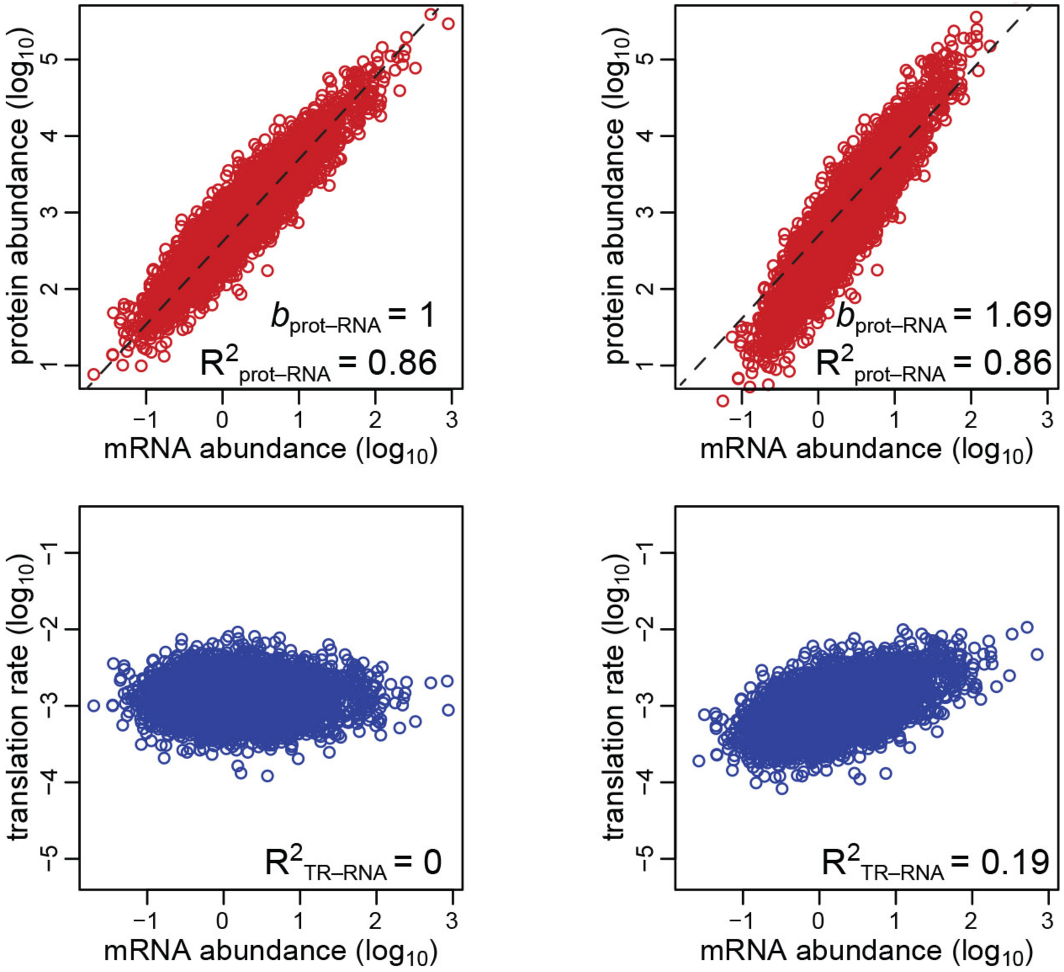
Li et al. (2017) NAR gkx898.

How can we estimate the contribution of translation rates to protein levels?



Li et al. (2017) NAR gkx898.

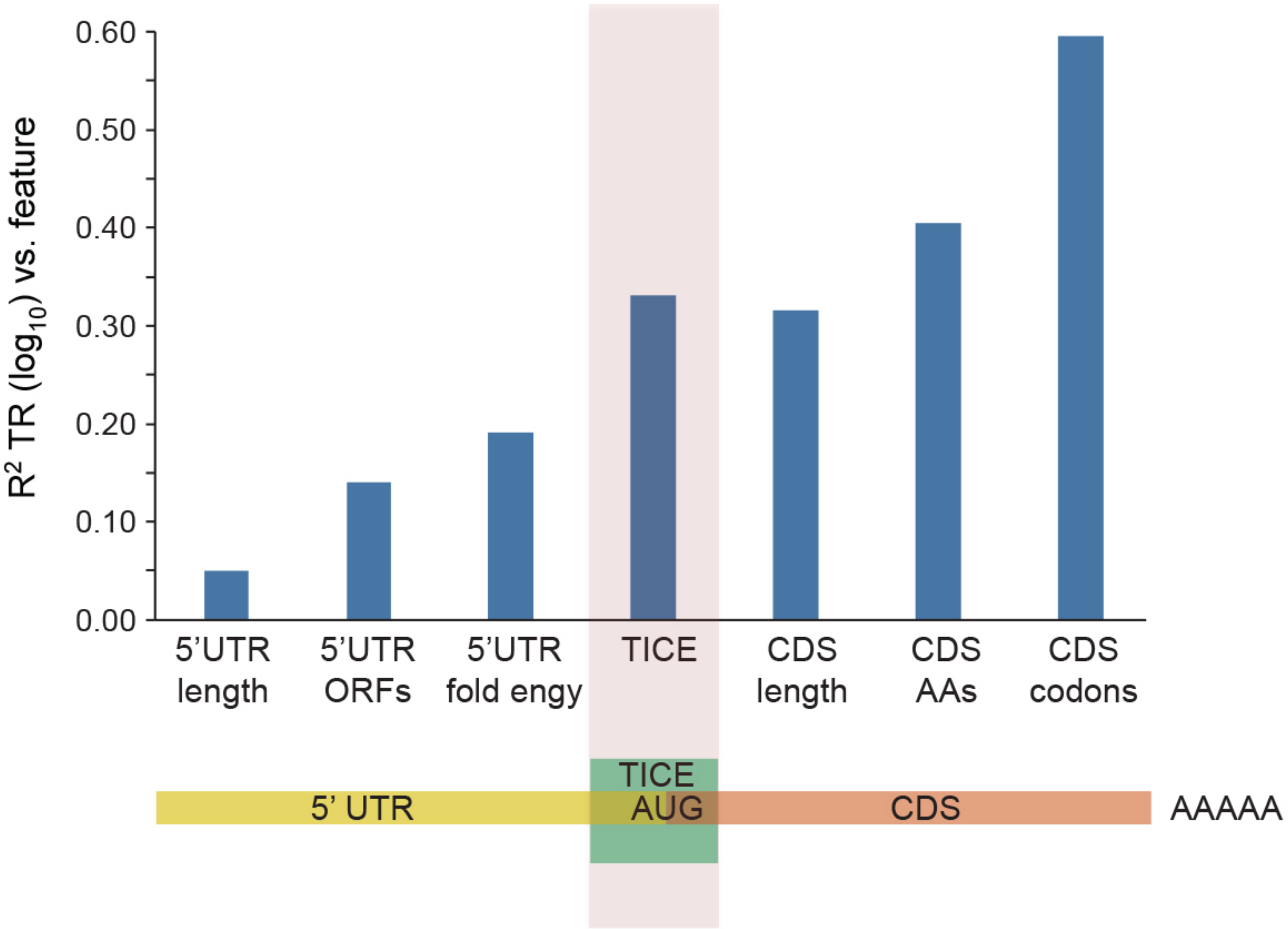
The Contributions of General Translational Control Sequences



Translation does not correlate with mRNA

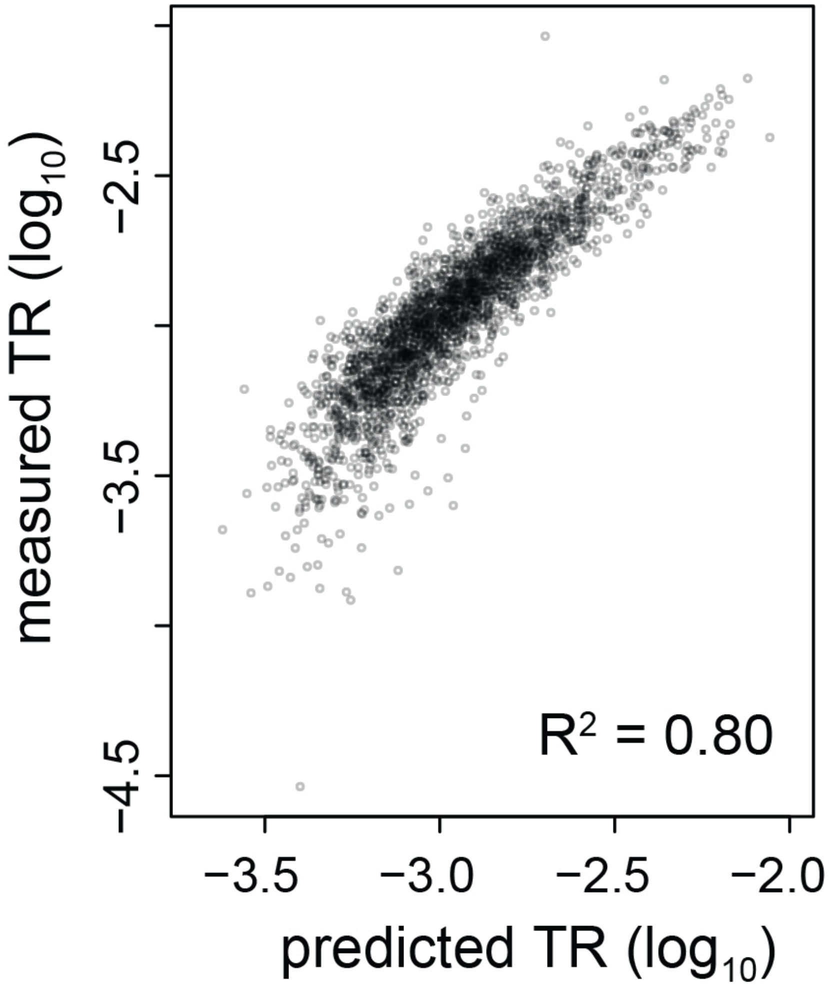
Translation partially correlates with mRNA

Seven mRNA sequence features specify 80% of the variance in translation rates



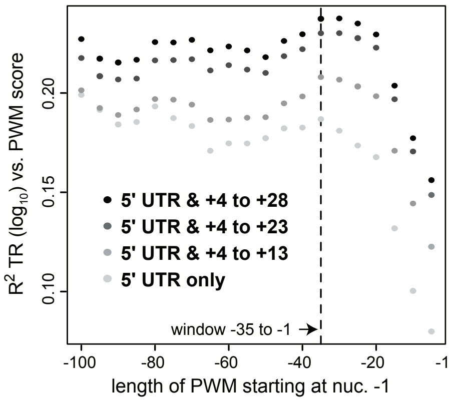
Li et al. (2017) NAR gkx898.

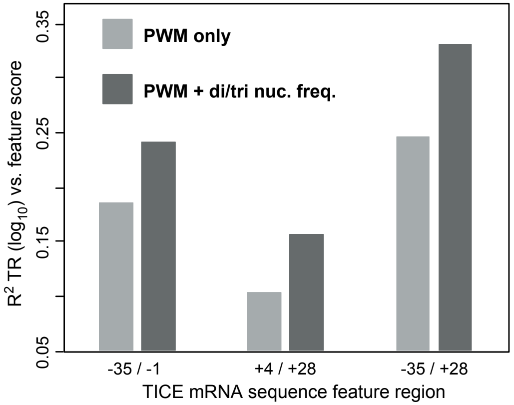
Seven mRNA sequence features specify 80% of the variance in translation rates

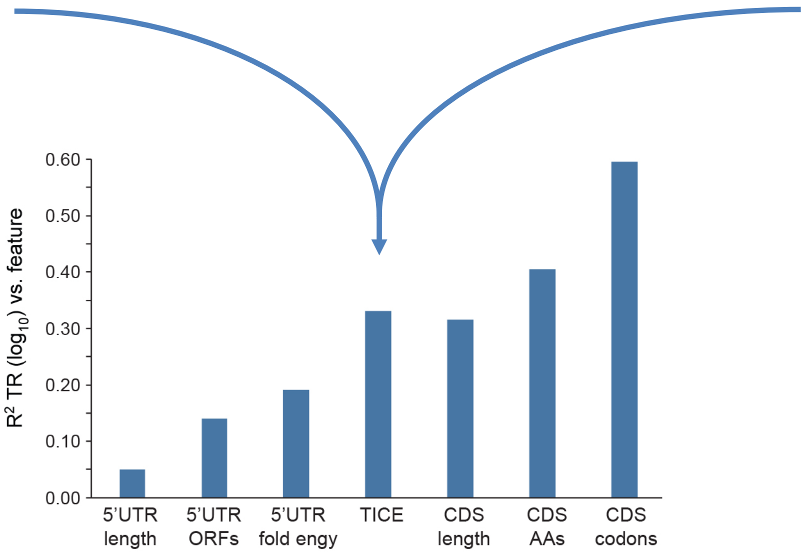


Li et al. (2017) NAR gkx898.

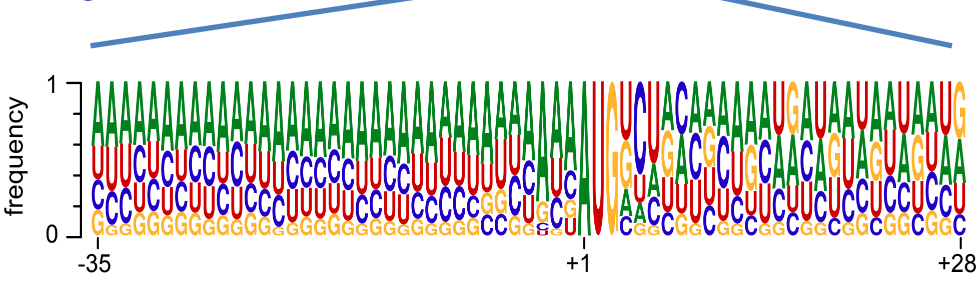
A Translation Initiation Control Element (TICE) spans -35 to +28







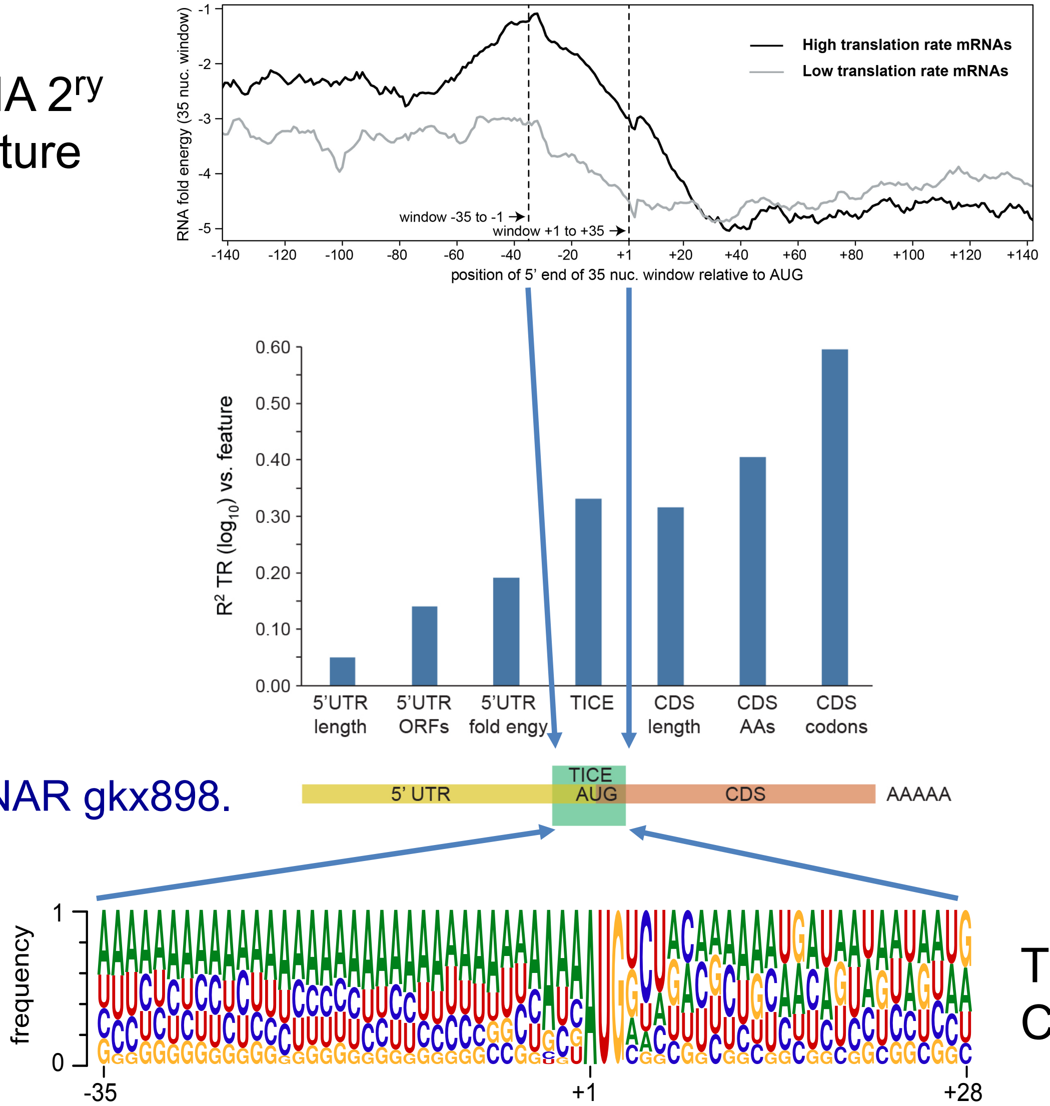
Li et al. (2017) NAR gkx898.



Translation Initiation Control Element (TICE)

A Translation Initiation Control Element (TICE) spans -35 to +28

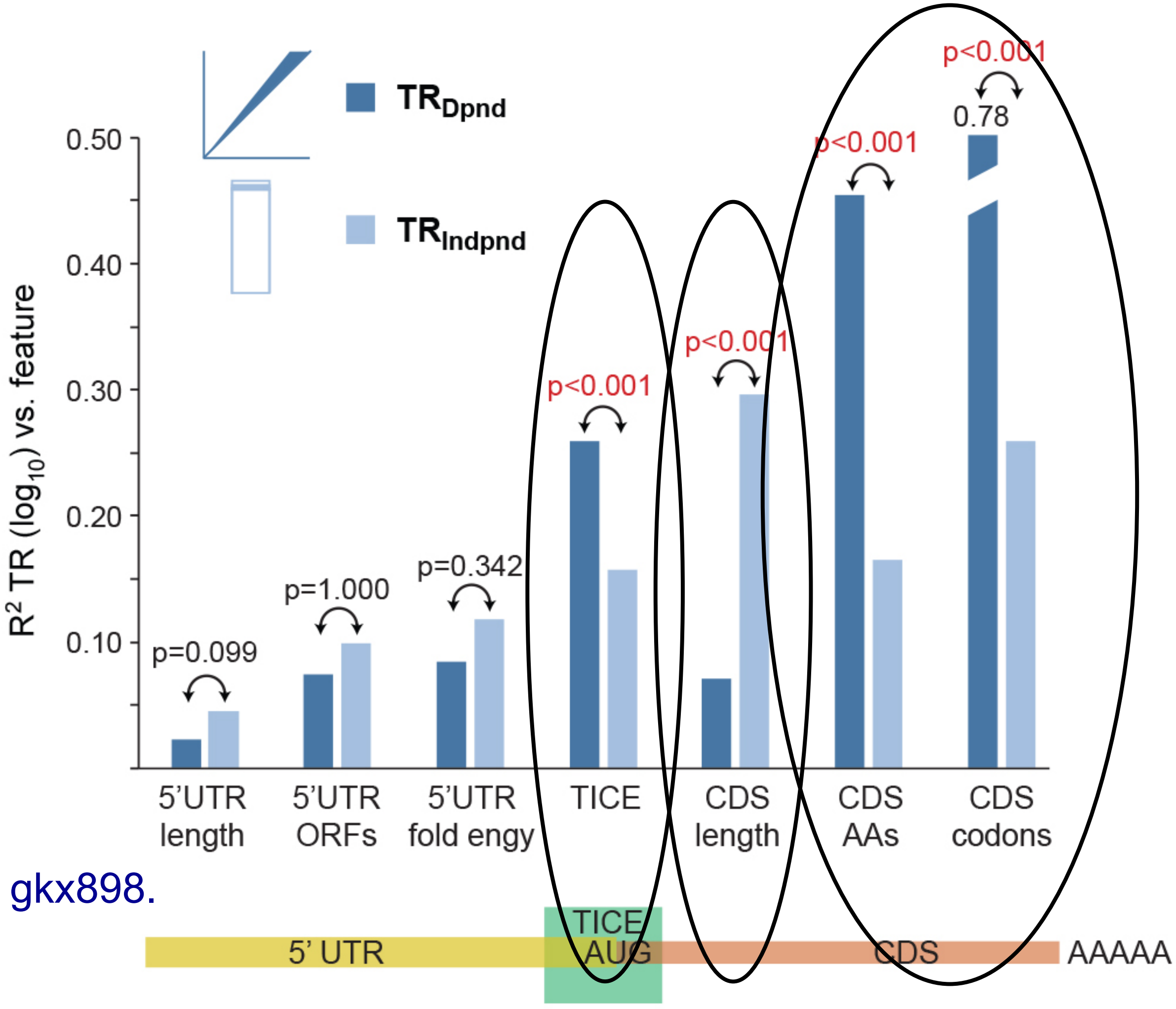
mRNA 2^{ry} structure



Li et al. (2017) NAR gkx898.

Translation Initiation Control Element (TICE)

mRNA sequence features differentially specify TR_{Dpnd} and TR_{Indpnd}



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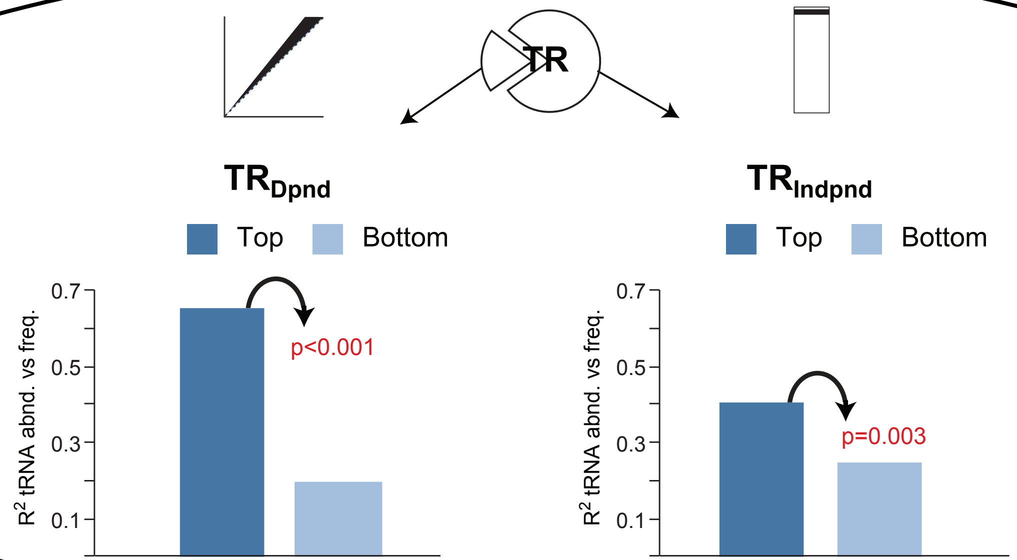
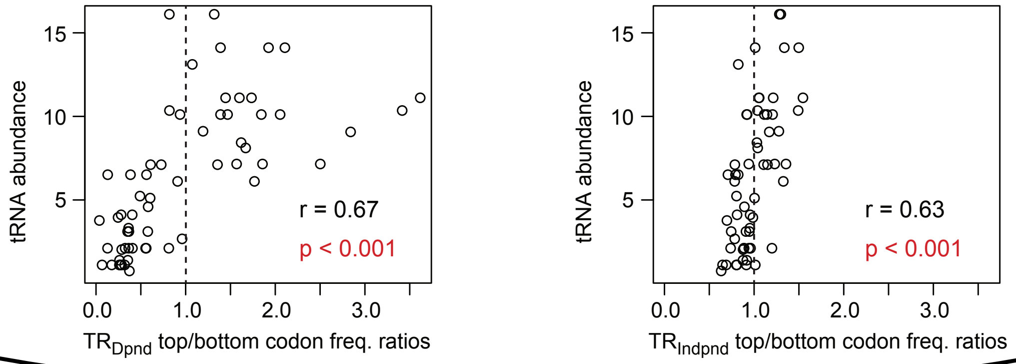
Codon frequency preferentially specifies TR_{Dpnd}

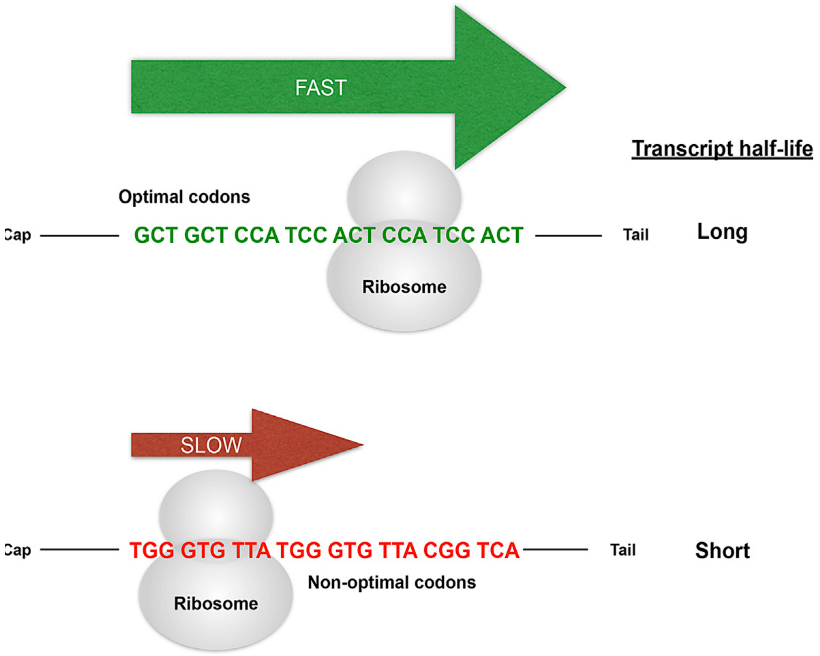


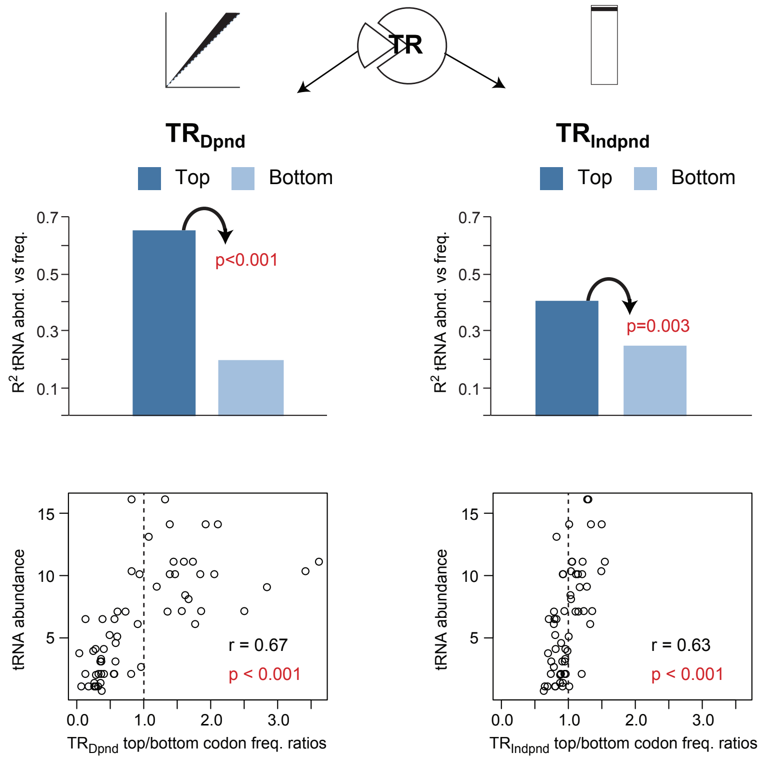


Codon frequency preferentially specifies TR_{Dpnd}

Codon usage increases mRNA stability

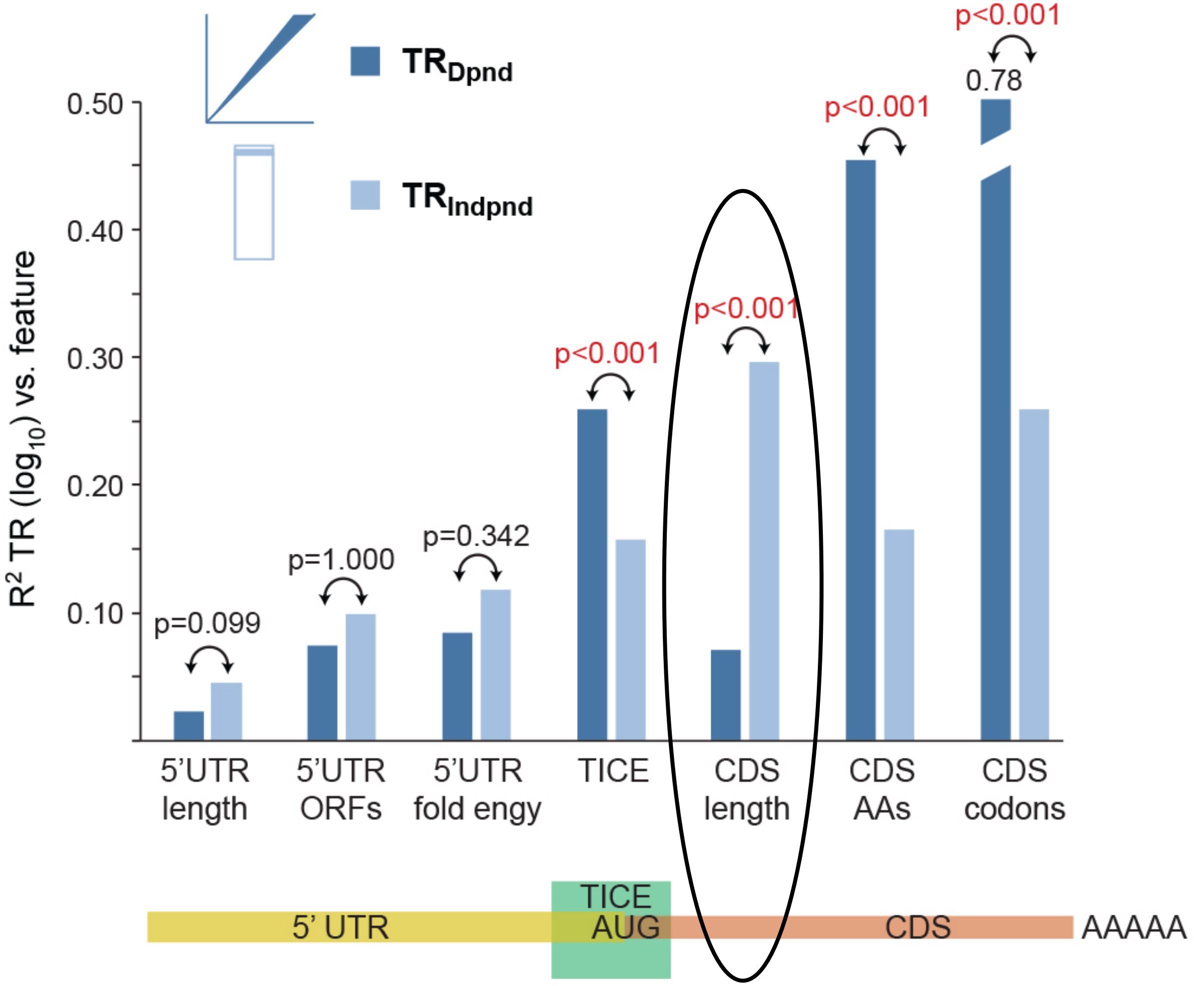
Therefore…...





Presnyak et al, 2015

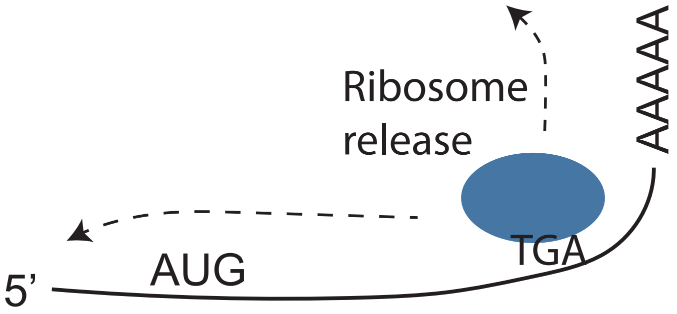
CDS length preferentially specifies TR_{Indpnd}



Li et al. (2017) NAR gkx898.

CDS length affects initiation rate

Short CDS



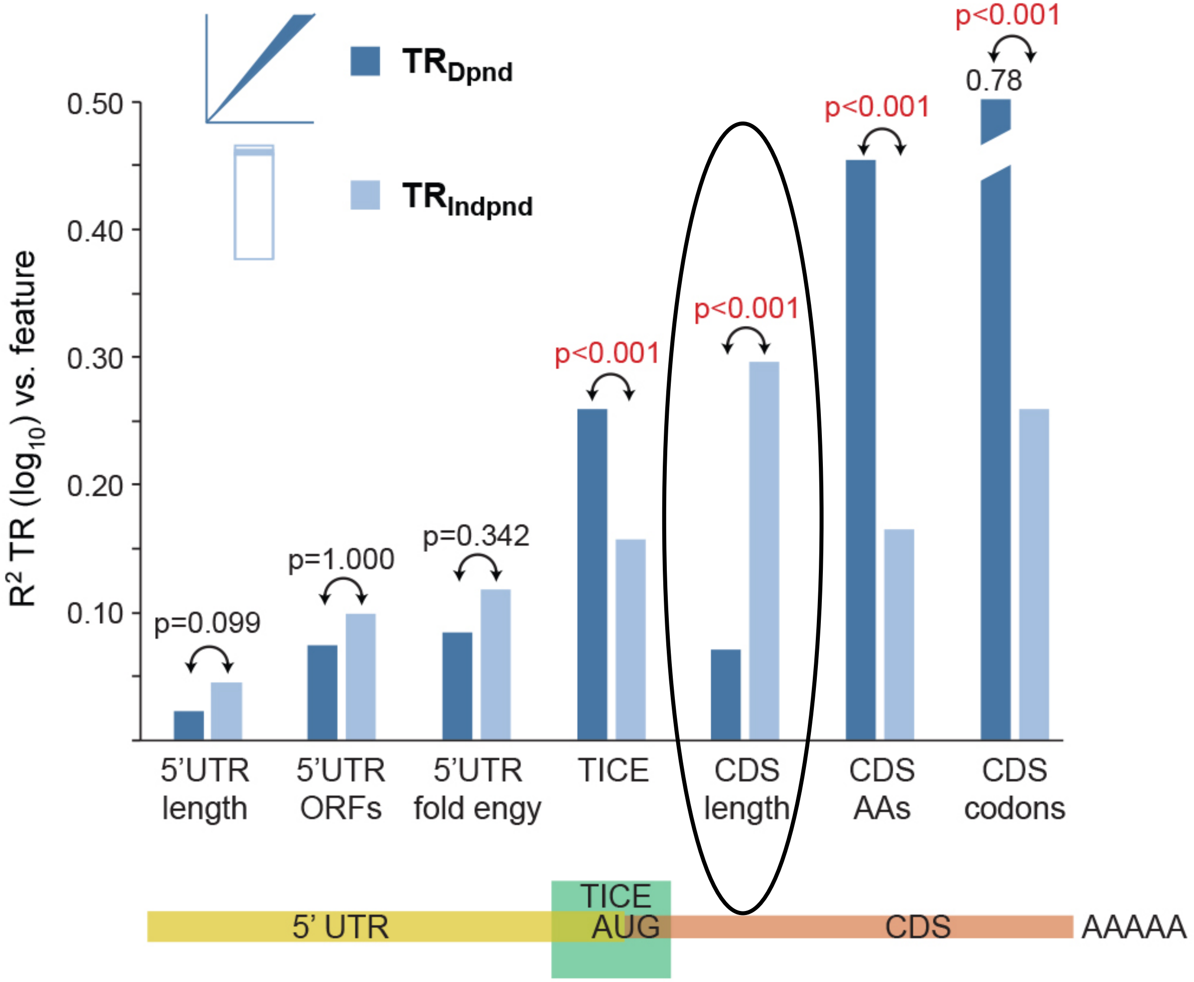
Efficient recapture of released ribosomes

Long CDS

Inefficient recapture of released ribosomes

Christensen et al. 1987; Arava et al, 2003; Thompson and Gilbert, 2016

CDS length preferentially specifies TR_{Indpnd}



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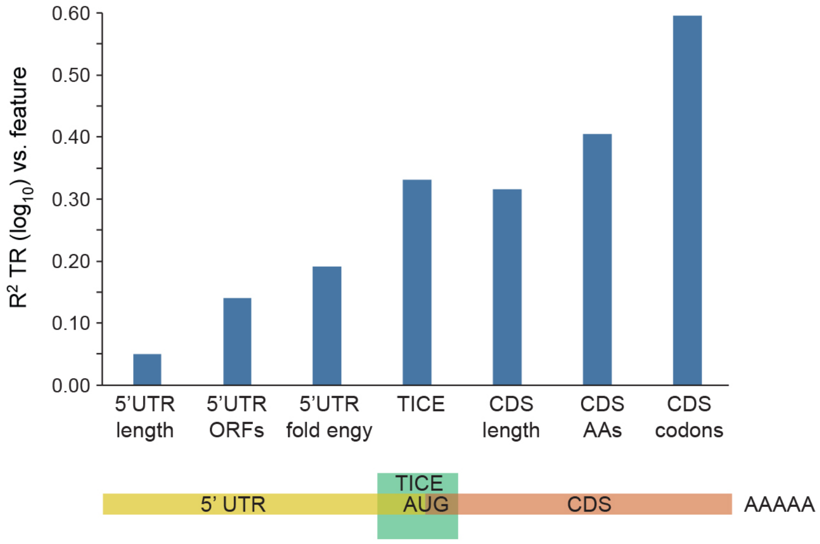
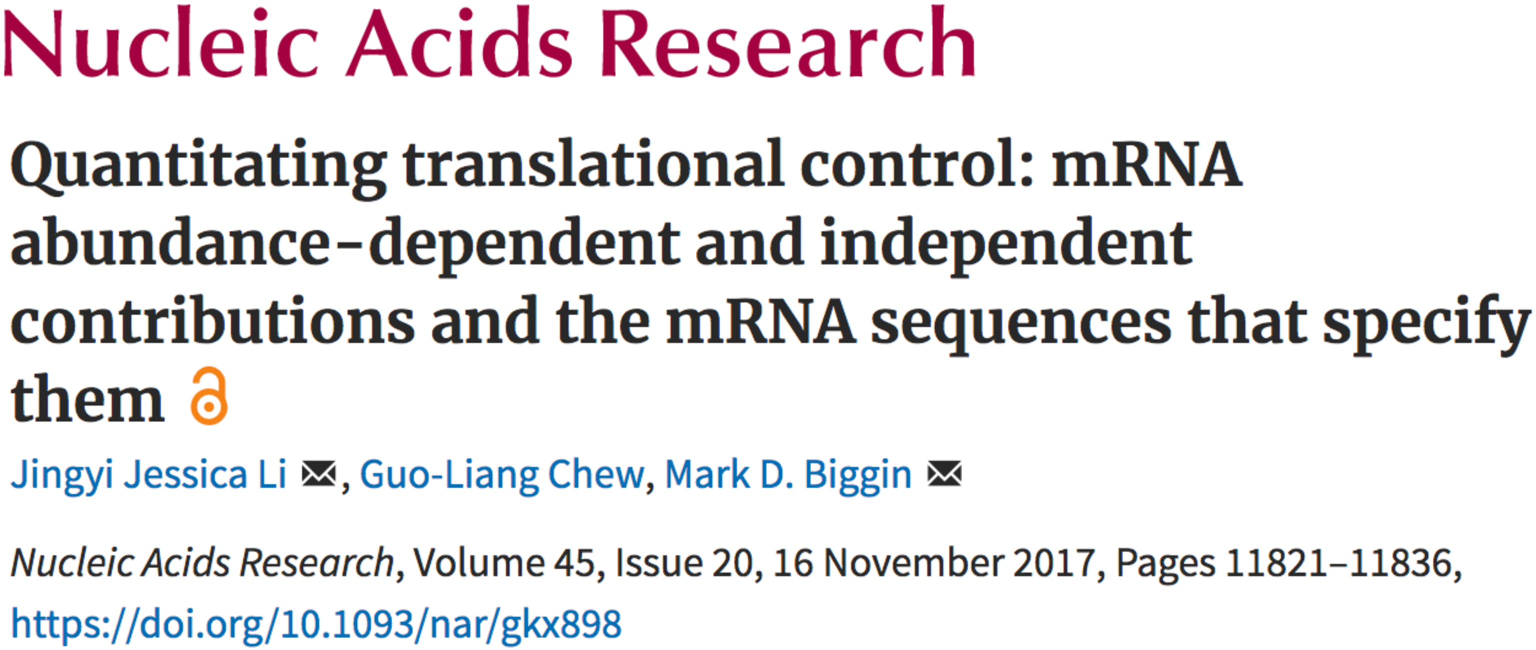
The Contributions of General Translational Control Sequences Across the Eukarya



SPECIES
S. cerevisae (yeast)
S. pombe (yeast)
A. thaliana (plant)
D. melanogaster (fruit fly)
M. musculus (mouse)
H. sapiens (human)



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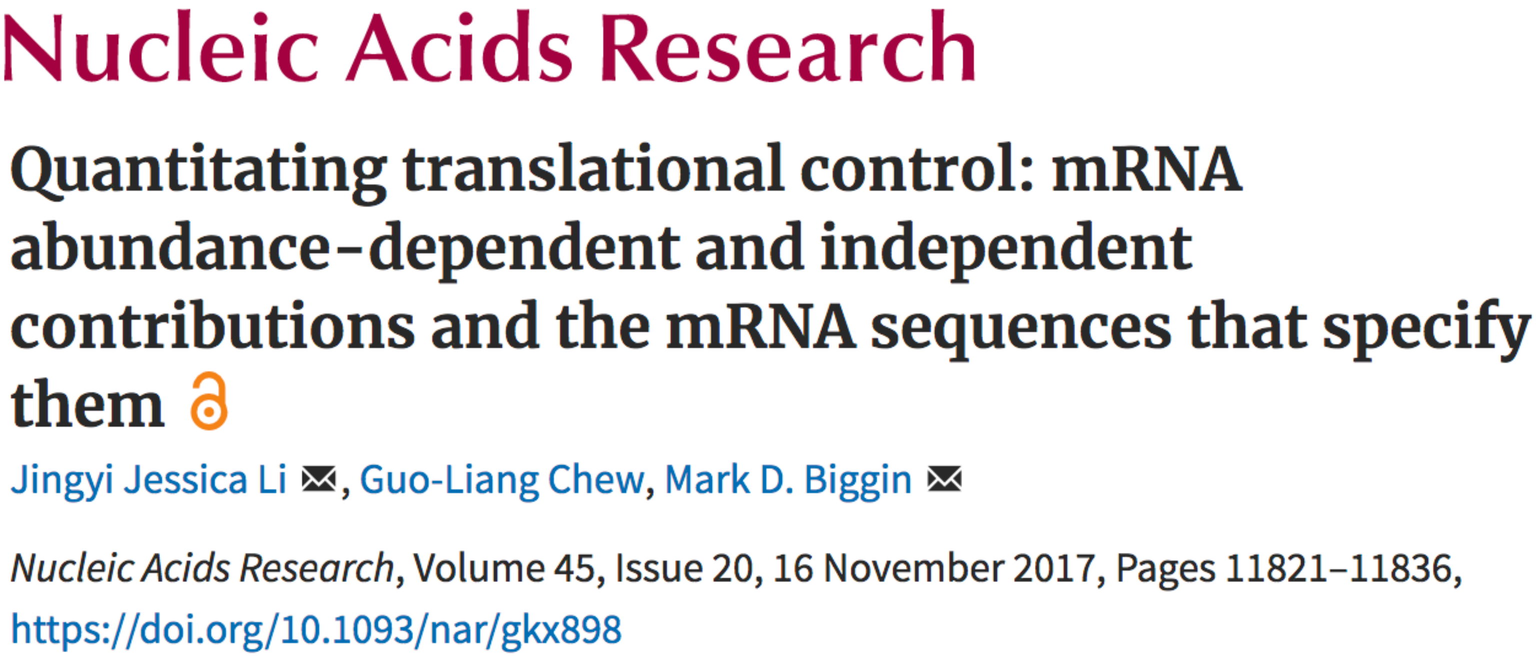

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