Stochastic interactions between ncRNAs and mRNAs inhibit translation and are selected against

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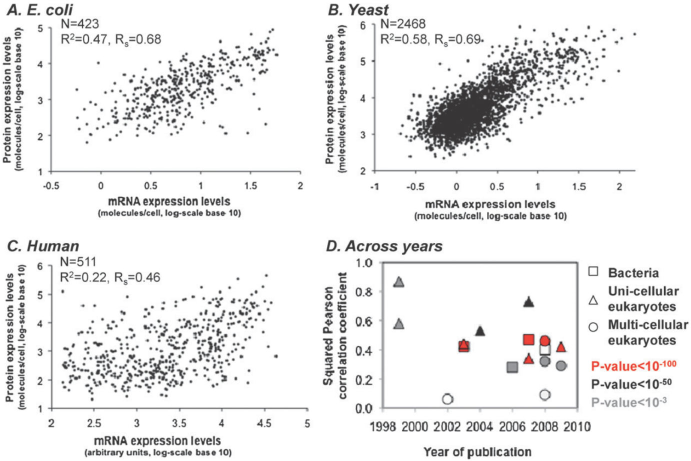
The hard work of Sinan Uğur Umu

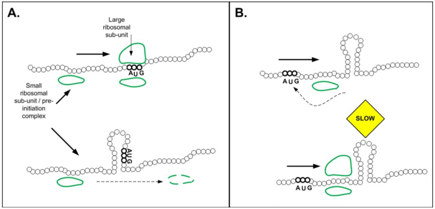
mRNA levels are poorly correlated with protein levels across domains of life



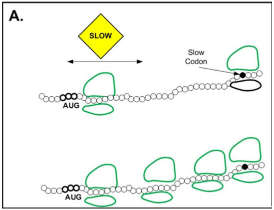
de Sousa Abreu, Penalva, Marcotte & Vogel (2009) Global signatures of protein and mRNA expression levels. *Molecular BioSystems.*

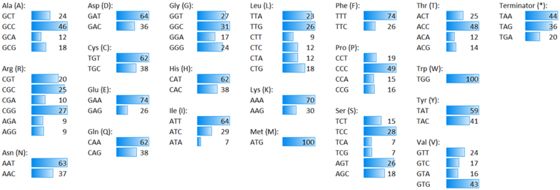
Currently only two general models of translation inhibition exist

- RNA structure



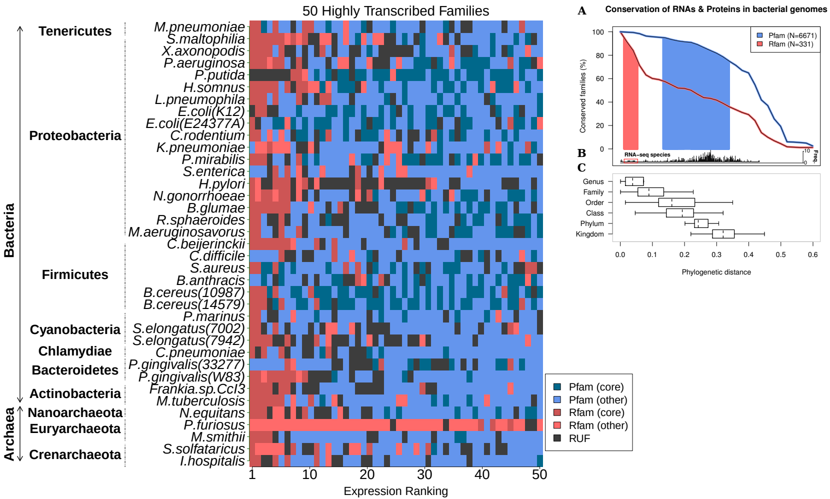
- Codon usage





Tuller & Zur (2015) Multiple roles of the coding sequence 5′ end in gene expression regulation. *Nucl. Acids Res.*

Non-coding RNAs are ubiquitous and abundant



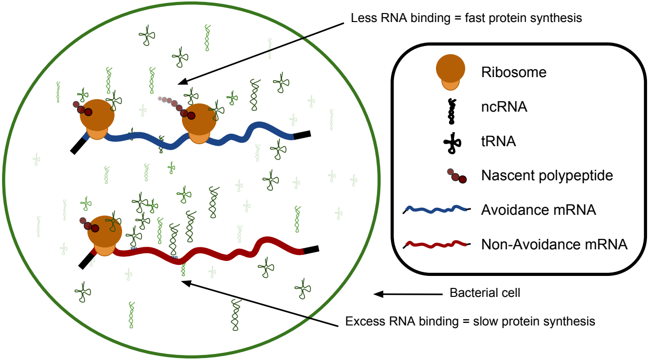
Lindgreen *et al.* (2014) Robust Identification of Noncoding RNA from Transcriptomes Requires Phylogenetically-Informed Sampling. *PLOS Computational Biology.*

Functionally characterising RUFs

- RUFs are some of the most abundant transcripts in the cell
- General approaches for functional characterisation are hard and has been largely unsuccessful, trying:
  - Comparative RNA-seq
  - Motif annotation with RMfam
  - Synteny information
  - Checking potential RNA:RNA interactions

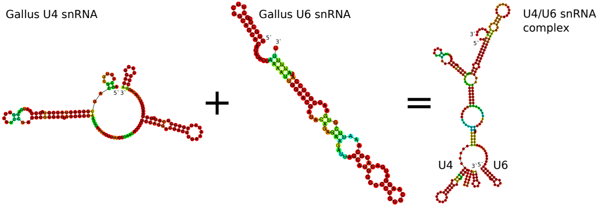
Do ubiquitous and abundant RNAs influence translation?

- Given that ncRNAs like rRNA & tRNA, RNase P RNA, SRP RNA, tmRNA and 6S RNA are among the most abundant RNAs in the cell ($[ncRNA] >> [mRNA]$)
- AND that RNAs are sticky (like to hybridise)
- THEN maybe stochastic interactions with mRNAs inhibit translation



How can this hypothesis be tested?

- An accurate hybridisation prediction method:
    - RNAup: nearest neighbour model, computes unfolding as well as hybridisation energy
- Focus on 6 RNA families & 114 proteins that are highly conserved. Test the 1st 21 nucleotides of CDS (critical region & saves LOTS of compute)
- We predict that: (**1**) there will is selection against ncRNA:mRNA interactions
- and (**2**) that ncRNA:mRNA interactions will influence [protein]:[mRNA] ratios

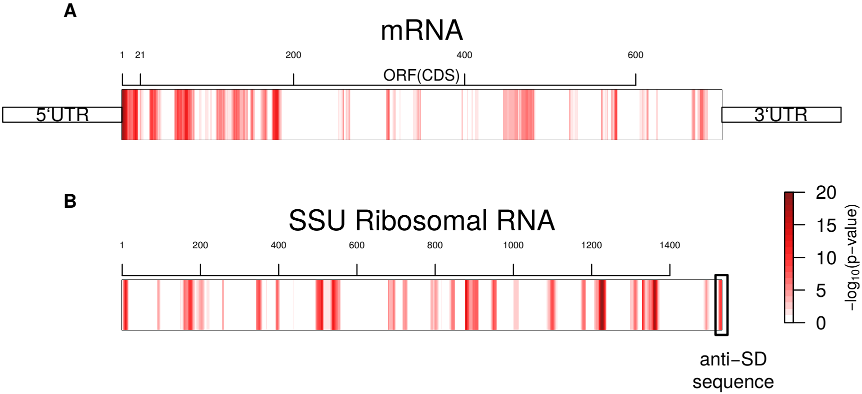


ΔG = -39.70 kcal/mol

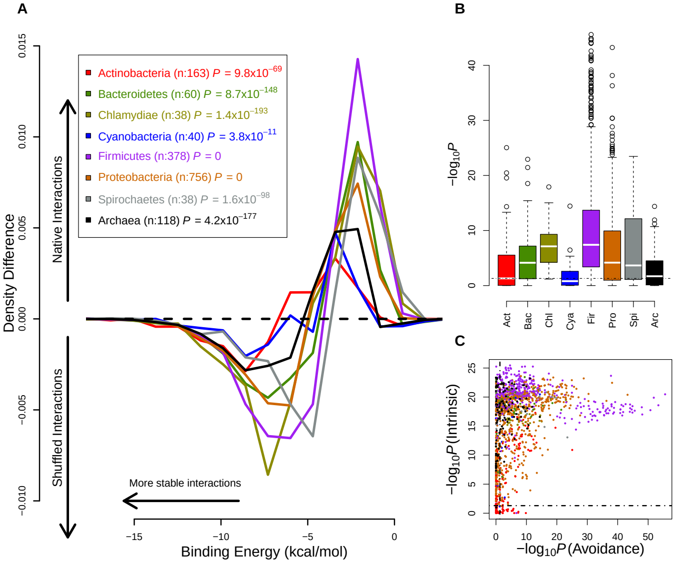
ΔG = -32.60 kcal/mol

ΔG = -73.80 + 13.10 + 19.10
= -41.6 kcal/mol

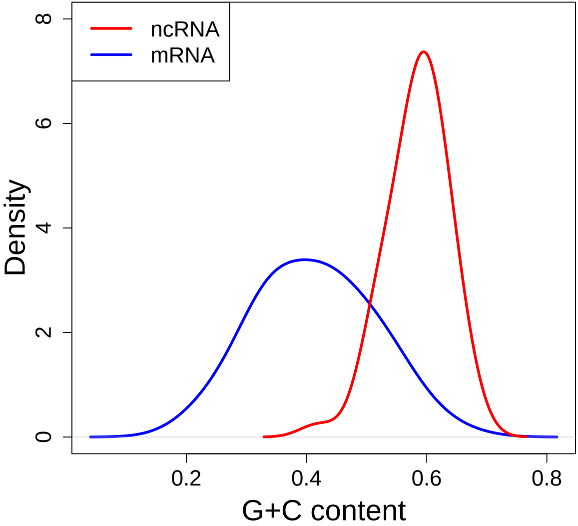
Justifying 1:21



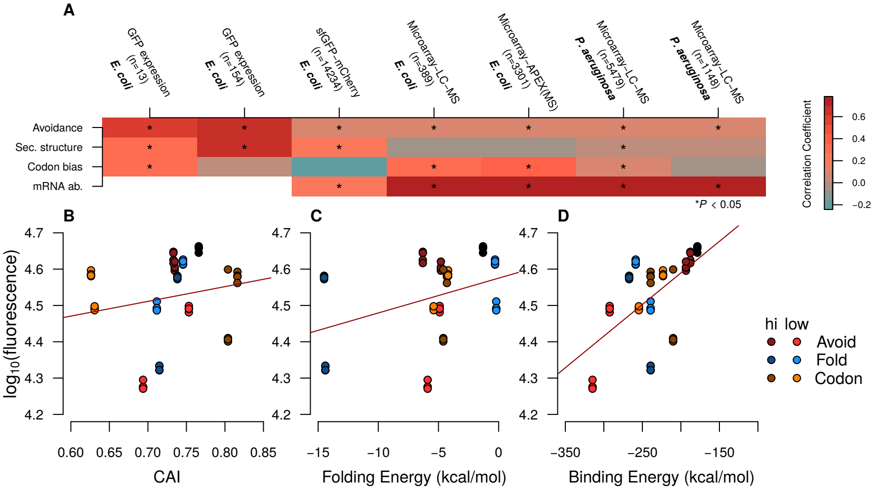
Are ncRNA:mRNA interactions selected against?



"Intrinsic" avoidance: *E. coli*



Do ncRNA:mRNA interactions influence protein expression?



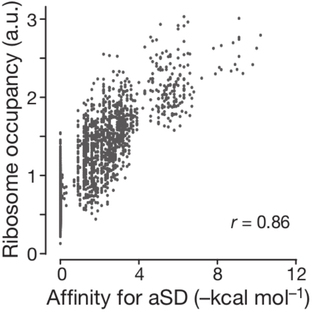
CAI: $R_s = 0.29$, $P = 0.016$; Sec. Struct.: $R_s = 0.34$, $P = 0.006$; Avoidance: $R_s = 0.56$, $P = 6.9x10^{-6}$

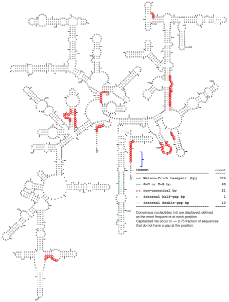
A specific case of ncRNA:mRNA interactions influencing protein expression

doi:10.1038/nature10965

The anti-Shine–Dalgarno sequence drives translational pausing and codon choice in bacteria

Gene-Wei Li[1], Eugene Oh[1] & Jonathan S. Weissman[1]





Li, Oh & Weissman (2012) The anti-ShineDalgarno sequence drives translational pausing and codon choice in bacteria. *Nature.*

Conclusion & Further Work

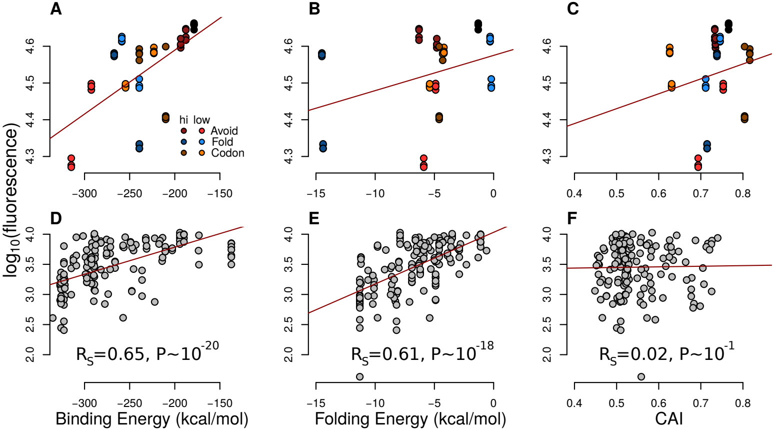
- Can we detect negative selection against ncRNA:mRNA interactions over evolutionary time-scales?
    - Yes!
- Can we determine if ncRNA:mRNA interactions influence protein expression?
    - Yes! $\sim$ 42% of variation in GFP expression, 0.8-1.2% in native data
- Further work:
    - Do ncRNA:mRNA interactions influence viral infection, hybridisation, HGT & transformation expts?
    - Do ncRNA:mRNA interactions influence Eukaryotic gene expression?
    - Are ncRNA:mRNA interactions a driver of compartmentalisation?

Thanks & Plugs

- Sinan Uğur Umu
- Anthony Poole & Renwick Dobson

- Rfam/RNAcentral are hiring:
  - Project Leader
  - Software Developer
  - Database Biocurator

Effect sizes & scatter plots



Kudla, Murray, Tollervey, Plotkin (2009) Coding-sequence determinants of gene expression in Escherichia coli. *Science.*