

Codon Bias Is a Factor in Regulating Expression via Translation Efficiency in the Human Genome

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(1) Introduction:

Codon bias, the unequal use of synonymous codons, appears in many organisms. In different species, such as bacteria, yeast, nematodes and flies, codon bias has been shown to be not only a result of mutational drift, but also of natural selection acting for translation efficiency in highly expressed genes. So far, despite some evidence relating codon bias with gene expression levels, this action has not been confirmed in mammals.

(2) Objectives:

- Study the relations between codon bias, gene expression level, tRNA-gene copy numbers and amino acid characteristics, in order to find out whether codon bias in the human genome is driven by selection.
- Show that selection may act on codon bias in different ways depending on the expression level of a gene, and the biosynthetic cost of producing the corresponding protein.

(3) Methods:

Residual Codon Bias (RCB)

$$RCB(g) = \sum_i f_{aa(i)}(g) | f_i^g - E_i^{nc}(g) |$$

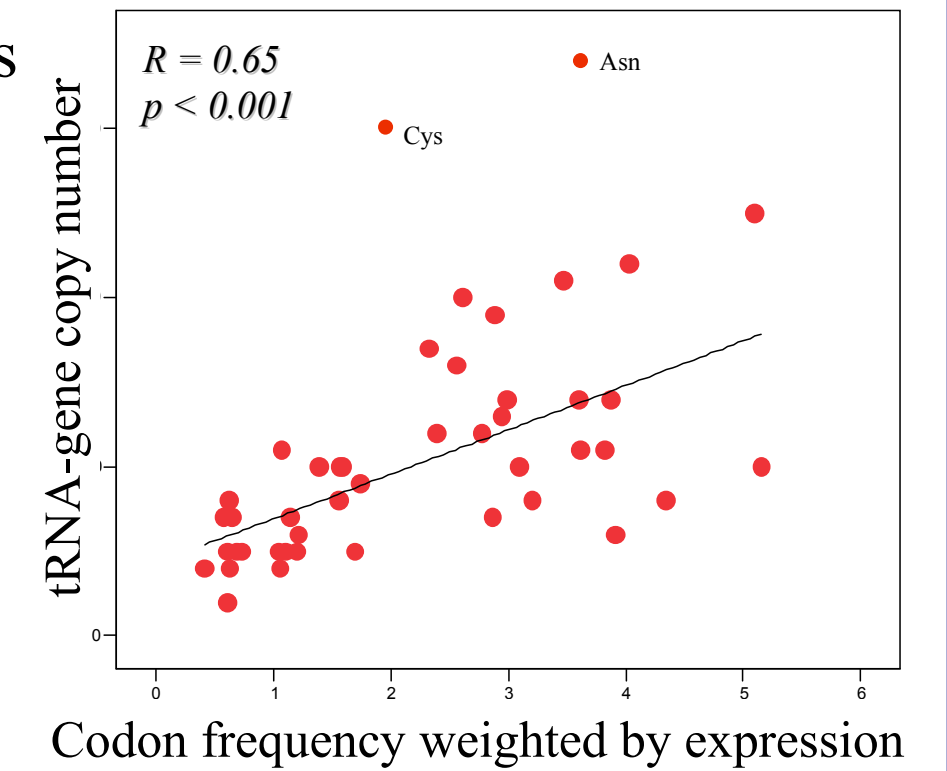
codon $\rightarrow i$ observed frequency of amino acid coded by i in g expected frequency of i in g , as calculated from introns and flanking regions

Corrected RSCU

$$cRSCU_i^g = \frac{f_i^g}{E_i^{nc}(g)}$$

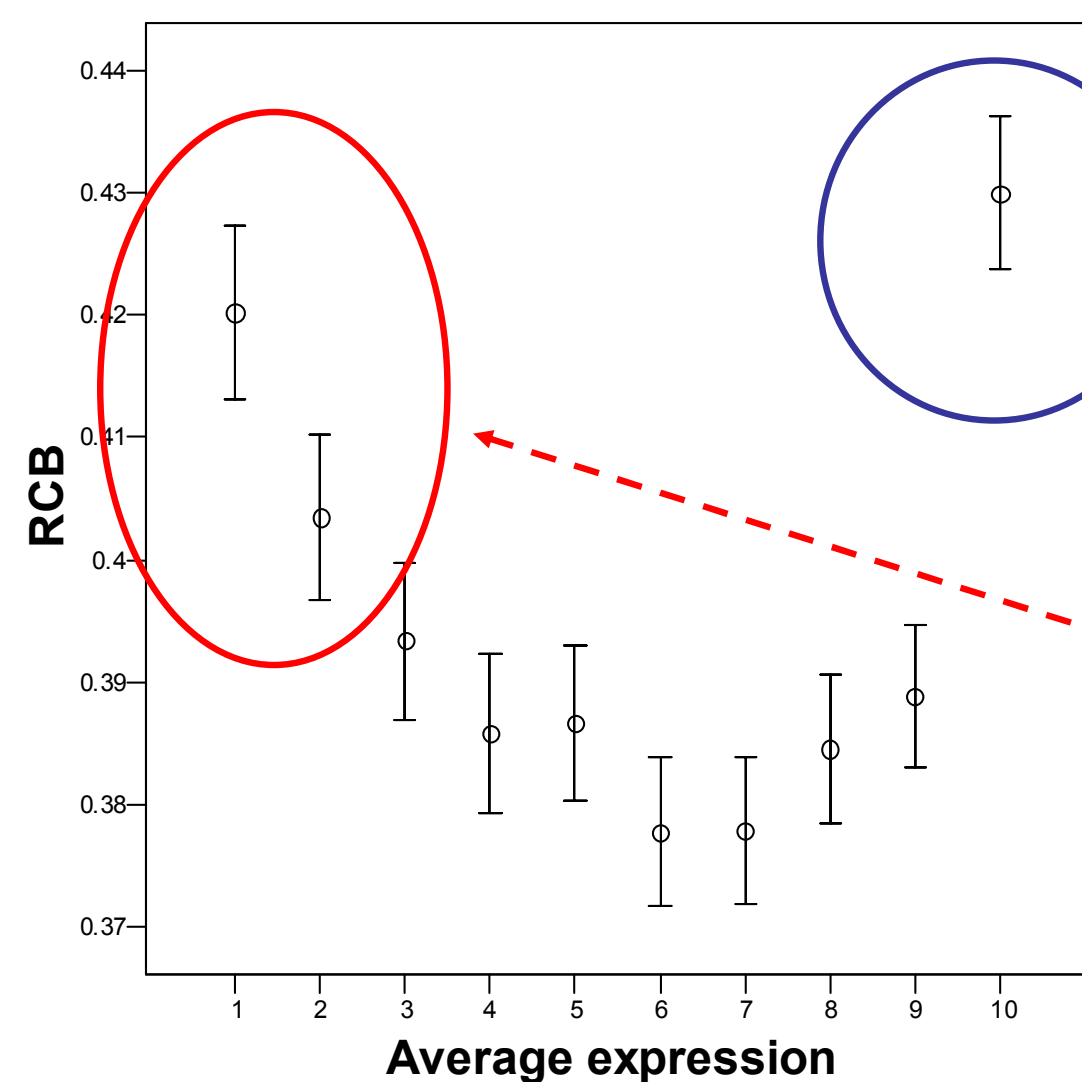
observed frequency of i in g expected frequency of i in g

The following analysis indicates that *gene copy numbers* can be used as a measure for tRNA abundance.



(4) Results:

1. Codon bias and expression level



Hypothesis:

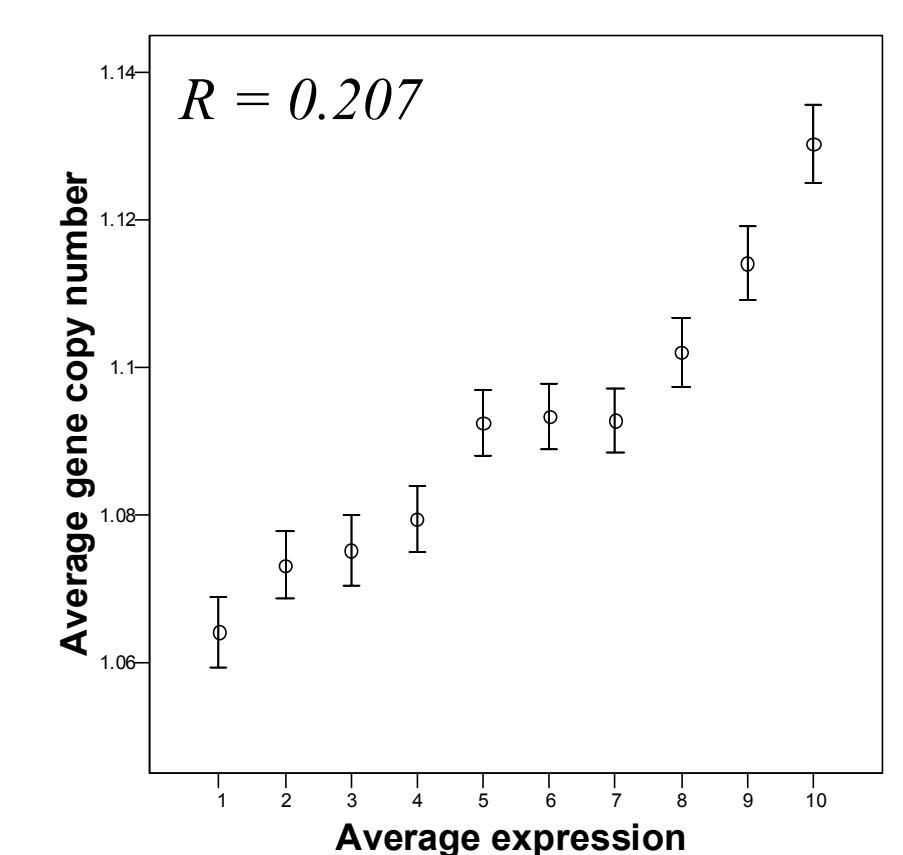
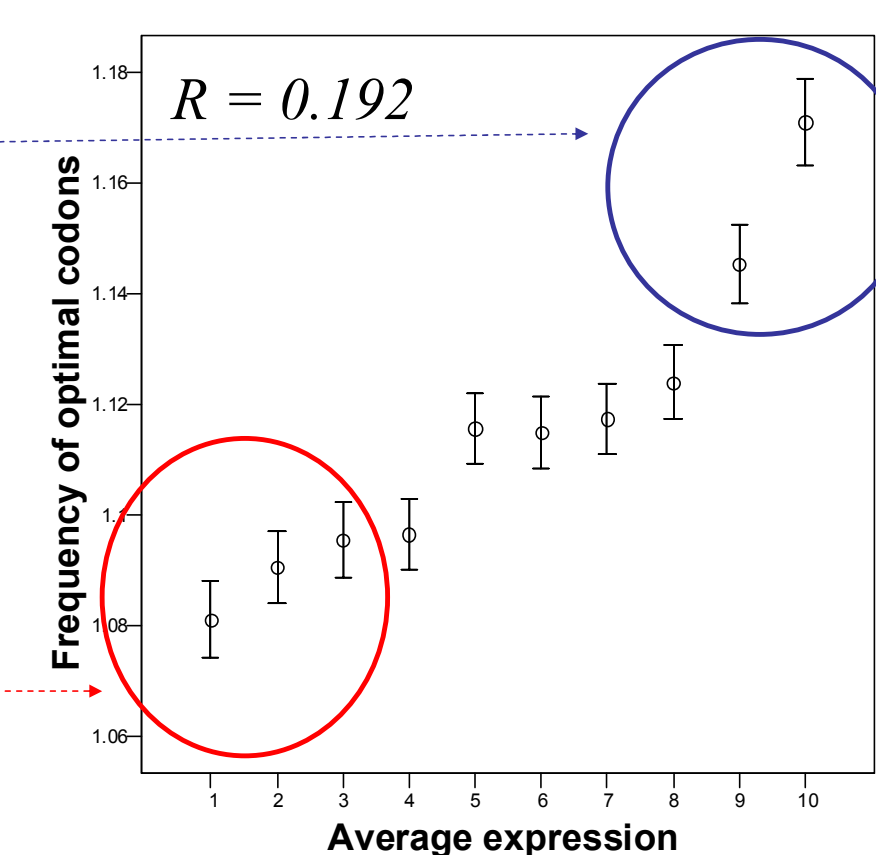
Two different codon biases:

High codon bias in highly expressed genes favors codons with high tRNA abundance, enhancing translation efficiency

High codon bias in certain lowly expressed genes favors codons with low tRNA abundance, enabling translation regulation.

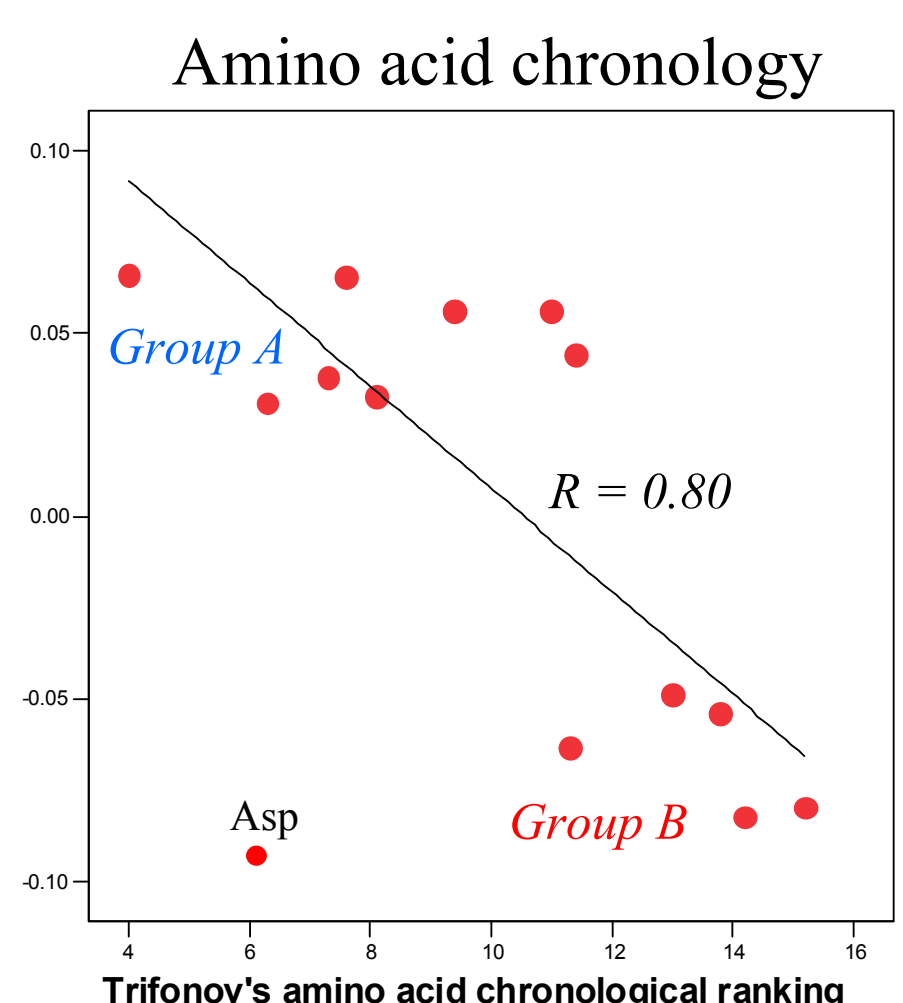
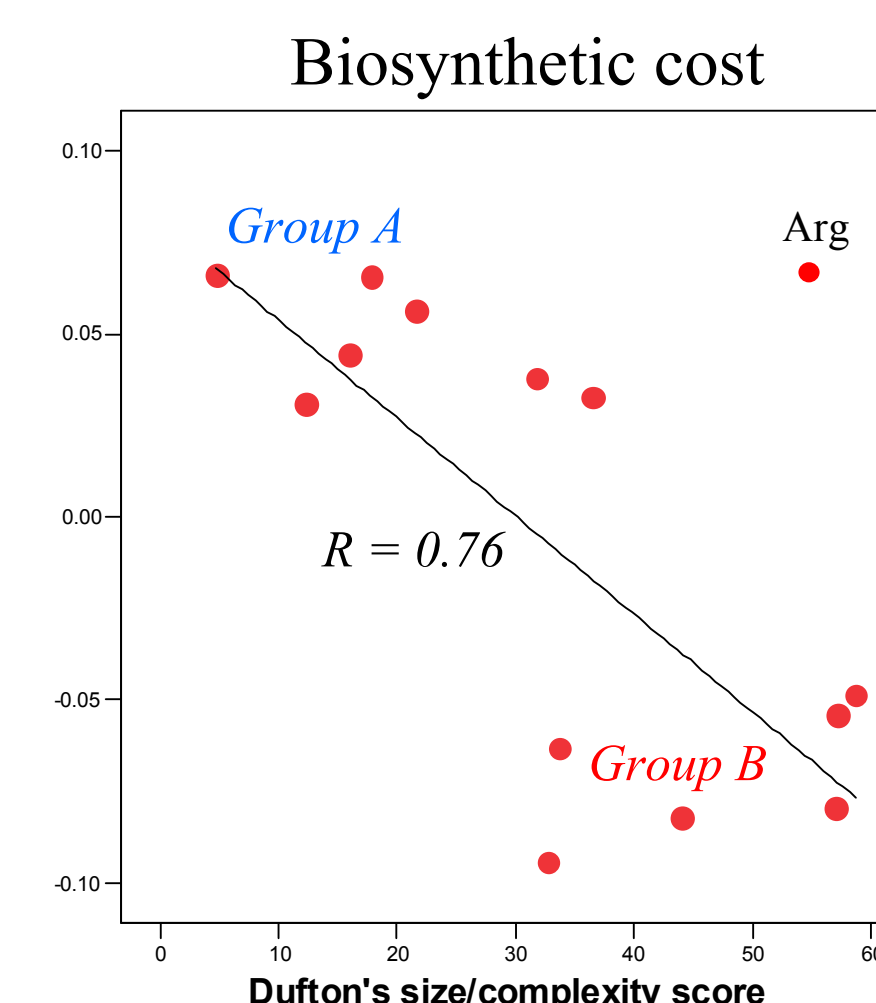
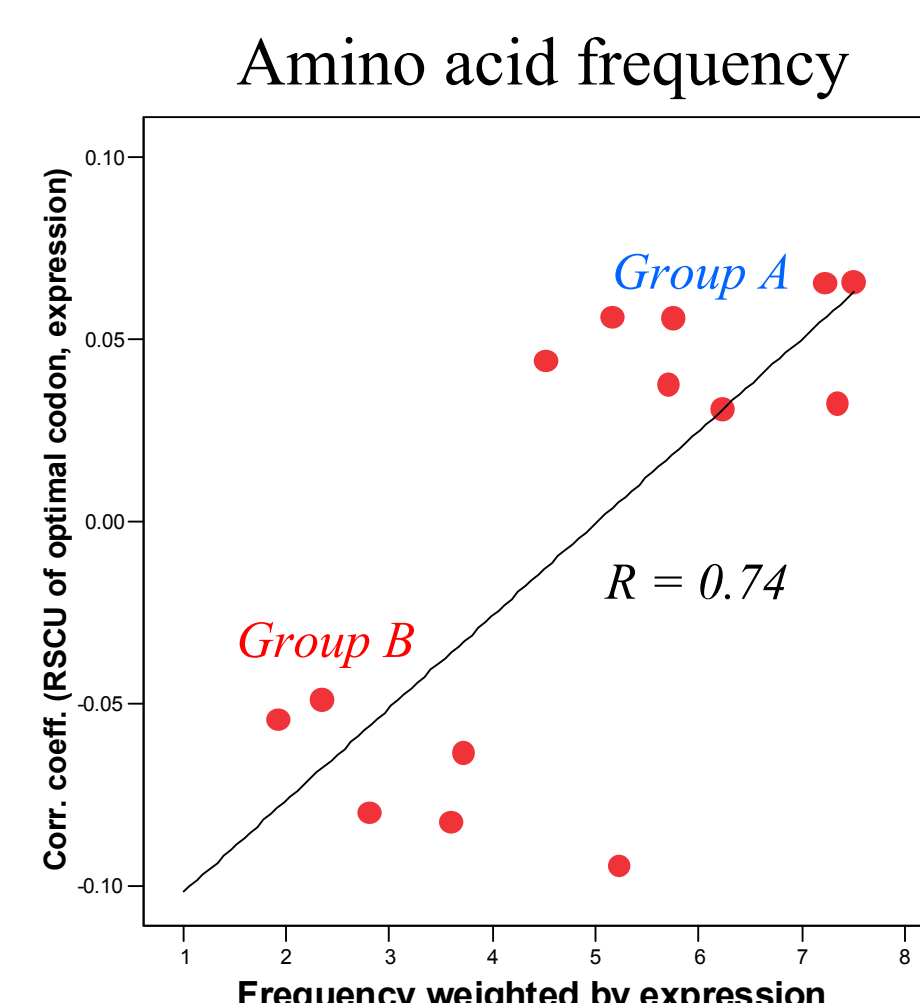
Evidence:

The number of tRNA genes rises with expression level

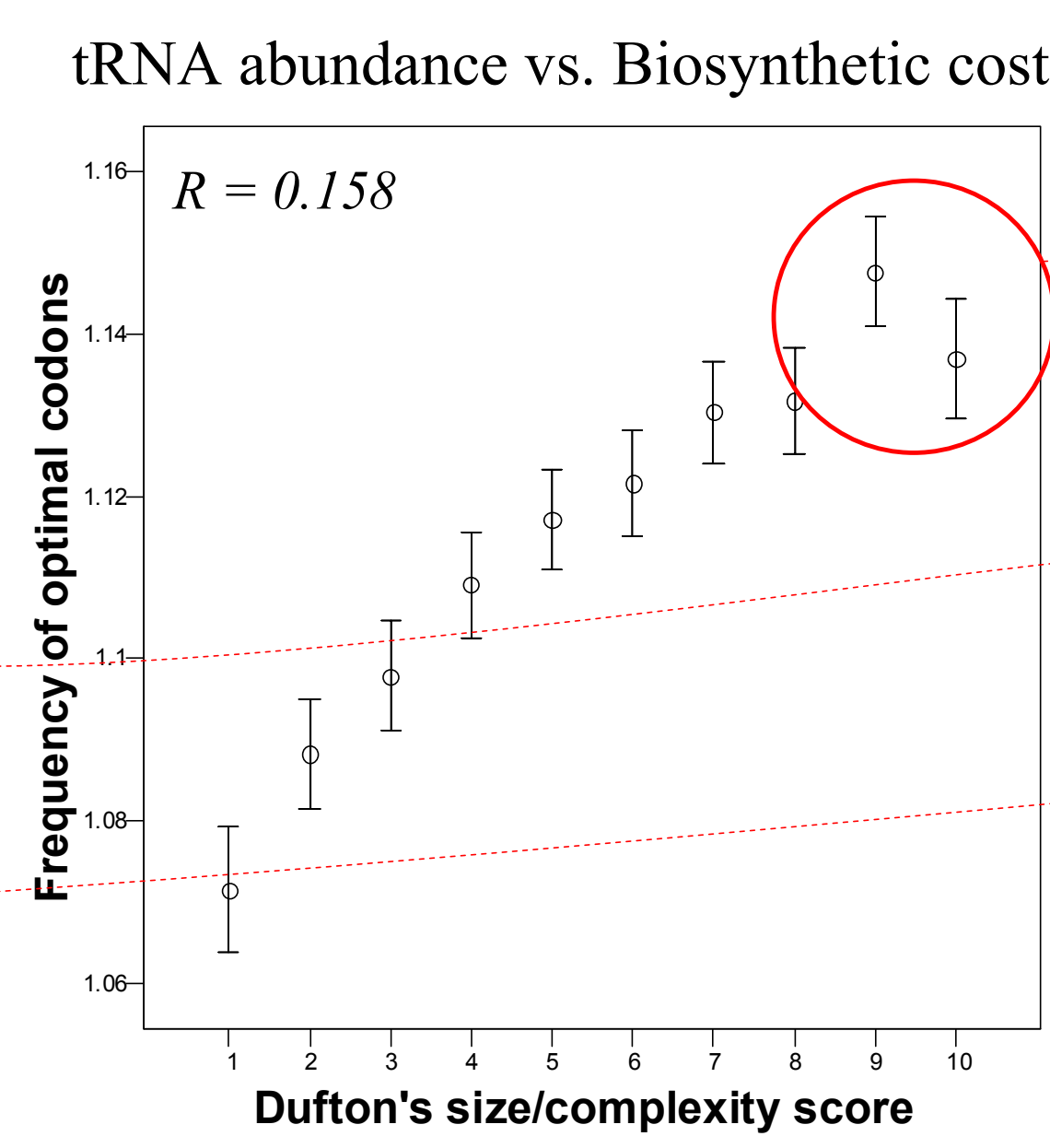
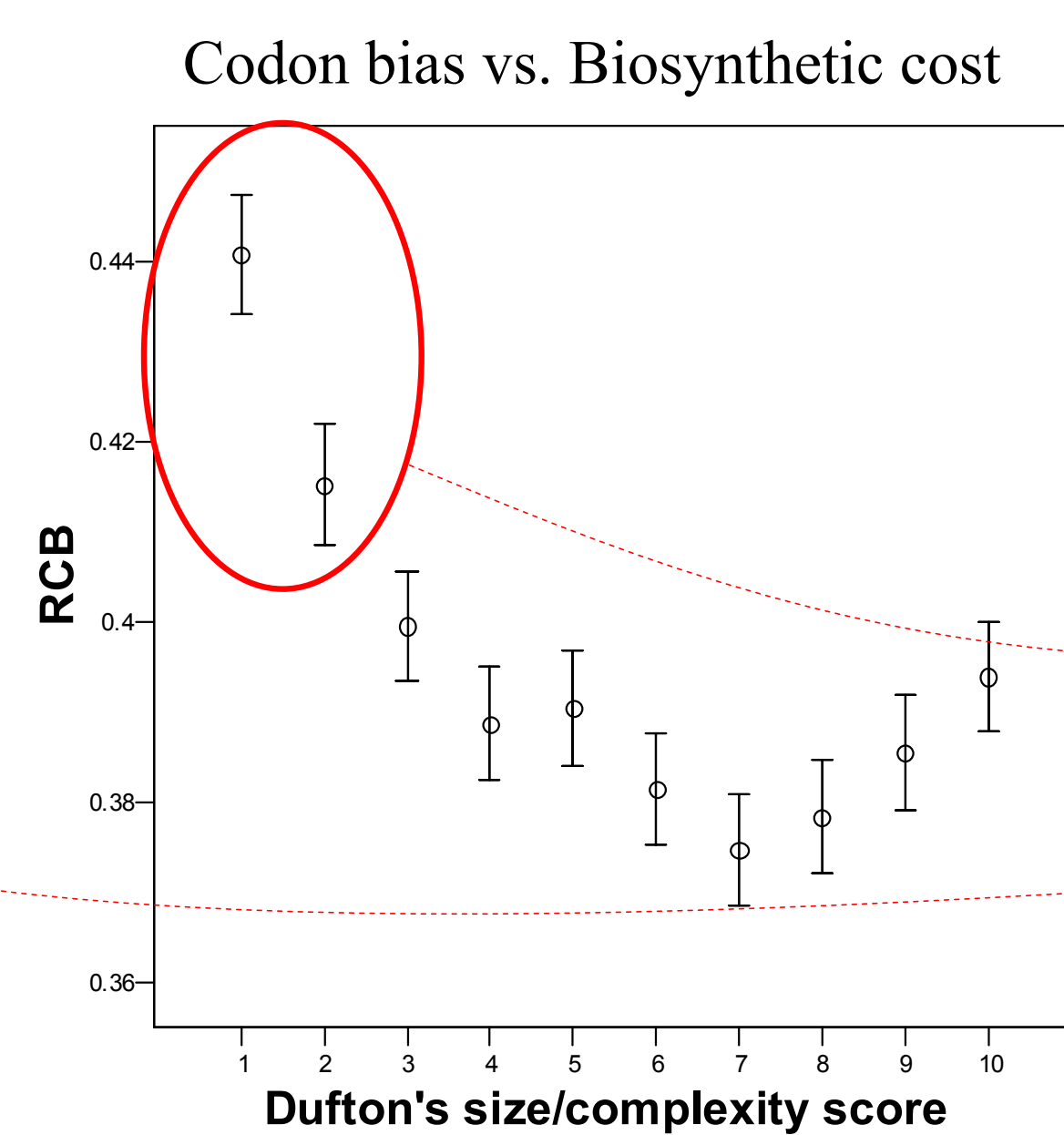
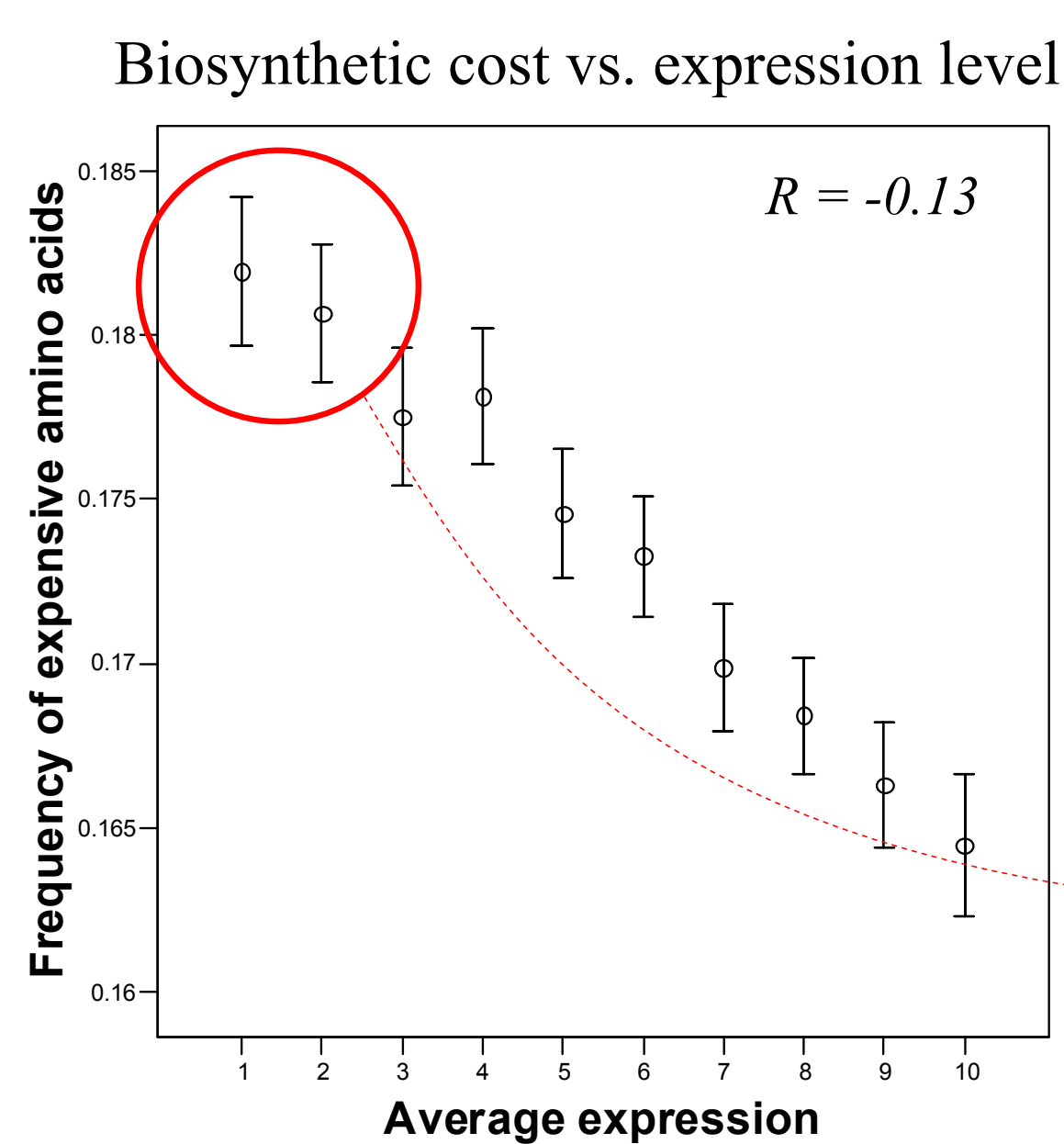


2. Amino acid and codon analysis:

	Group A	Group B	Group C
RSCU of optimal codon vs. expression	+	-	Not significant
Amino acids	Ala Arg Glu Ile Pro Ser Thr Val	Asn Asp Cys His Phe Tyr	Gln Gly Leu Lys



3. Codon bias and biosynthetic cost



High codon bias in some lowly expressed genes, encoding for expensive proteins, favors codons with high tRNA abundance for more accurate translation.

(5) Discussion

Three mechanisms can explain the weak action of selection on codon bias:

(I) Translation efficiency mechanisms:

High codon bias in highly expressed genes favors codons with high tRNA abundance, enhancing translation efficiency.

(II) Translation regulation mechanisms:

High codon bias in certain lowly expressed genes favors codons with low tRNA abundance, controlling elongation rate.

(III) Translation accuracy mechanism:

High codon bias in genes encoding for expensive proteins favors codons with high tRNA abundance, enabling more accurate translation.

Codon choice in simple, more frequent and more ancient amino acids tends to follow mechanisms I and II more than III, while in other amino acids the three mechanism may apply contradicting forces. These contradicting forces result in weak correlations. These correlations, however weak, are consistent, and are obtained regardless of the method in which codon bias is calculated, and the way it is corrected for background nucleotide content.