

## *Hypothesis*

# On the physico-chemical rationale of the genetic code

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We analysed two different and seemingly independent aspects of protein biosynthesis: the primary structure of codons and the reactivity of aminoacyl groups. This analysis revealed that more reactive aminoacyl groups correspond to less stable codon-anticodon complexes. The possible meaning of such a correlation is discussed in terms of the kinetic proofreading theory.

## 1. INTRODUCTION

The question about the physico-chemical rationale of the genetic code arises from its universal nature. Indeed, with only a few exceptions, the triplet nucleotide code is conserved in all organisms living today. Several attempts have been made to postulate a stereochemical fit between a particular amino acid and its corresponding codon or anticodon [1–4]. However, all we know about the mechanism of protein biosynthesis, as it exists at present, does not support this sort of hypothesis. Nevertheless, it does not exclude the existence of some, so far not recognized principles which explain why a particular codon sequence codes for a given amino acid. In other words, the fact that the codon XYZ corresponds to amino acid xyz might not be ‘a frozen accident’ but may have a specific and rational meaning in the process of protein biosynthesis.

## 2. SOME GENERAL CONSIDERATIONS

Thermodynamic parameters of the codon-anticodon interaction within the ribosome are as

yet largely unclear. Complex formation studies between tRNAs with complementary anticodons [5,6] suggest that the stability of such duplexes is not solely a function of the content of G·C base pairs formed. It is believed that one of the functions of hypermodified bases next to anticodons of many tRNAs is in the ‘equalizing’ of the stability of otherwise largely differing complexes [7–9]. Nevertheless, a number of reports show that, in general, the stability of the codon-anticodon complex depends on the content of G·C base pairs [10–12].

Variability, although in a different aspect, can also be seen in the other functionally important part of tRNA. Namely, different aminoacyl groups differ considerably not only in their structure, but also in their reactivity as peptide acceptor groups [13]. Here, the phenomenon is most clearly shown for so-called minimal acceptors, i.e. aminoacylated adenine nucleotides [13,14]. Aminoacylated pentanucleotides behave seemingly more uniformly in concentration dependence assays. However, their important kinetic parameters ( $k_{\text{cat}}$  values) still differ significantly [15], suggesting that differences in the reactivity of various aminoacyl groups, although not easily detectable at the level of intact aminoacylated tRNAs, may well in-

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fluence the process of polypeptide synthesis in vivo.

Thus, we have now described in brief two functionally important regions of tRNA. It is clear that their variability helps to generate the diversity needed to decode 20 different amino acids. The question we ask below is whether these two types of parameters, codon composition on the one hand and chemical reactivity on the other, vary independently.

### 3. ACCEPTOR ACTIVITY AND THE STRUCTURE OF THE COGNATE CODON

Table 1 compares data about peptide acceptor activities of different aminoacyl groups and the primary structure of codons corresponding to these amino acids.

The genetic code is degenerate, so that usually more than one codon corresponds to the same amino acid. Therefore, several amino acids have codons differing in their G and C content, and can be found in different columns of table 1. For alanine, published acceptor activities disagree and therefore this amino acid also appears in different lines of the table. However, as a rule, published results by different laboratories do not vary considerably.

The table shows rather clearly that amino acids with extra high acceptor activity, such as Phe, Tyr, Lys and Met, correspond to codons containing no or only one guanine or cytosine. On the contrary, Gly, Trp, etc., having very low acceptor activity, correspond to codons allowing the formation of 2–3 G·C base pairs in their codon-anticodon complexes. Hence, the results presented in this table tend to form a diagonal, indicating that the stronger the codon-anticodon complex, the lower is the acceptor activity.

### 4. APPLICATION TO THE KINETIC PROOFREADING THEORY

Kinetic proofreading models [19,20] are now supported by several experimental results [21–24]. Although it is not clear yet, we assume that the kinetically limiting and irreversible step in the process of translation is the peptidyl transferase reaction.

During the first step (scheme 1), the aminoacyl

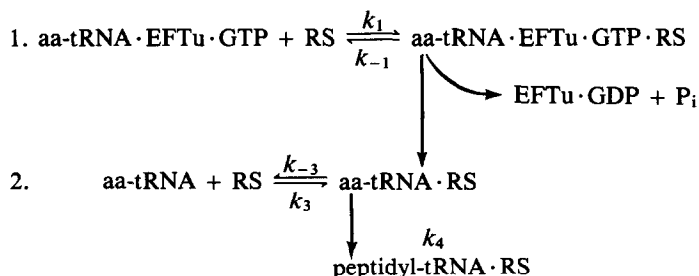
Table 1

Relationship between the number of G·C base pairs formed by codon-anticodon complexes of several tRNAs and acceptor activities of the corresponding aminoacyl moieties

Relative acceptor activity	Number of G·C base pairs formed			
	0	1	2	3
Very high	Phe Tyr Lys	Phe Tyr Lys Met		
High	Lys	Lys Met	Ala	Ala
Intermediate	Leu	Leu Ser Glu Val	Leu Ser Glu Val Pro	Pro
Low		Asp	Asp Ala Gly Trp	Ala Gly

References are as follows: Ala [13,14,16,17]; Asp [16]; Glu [16,17]; Gly [13,16]; Leu [13,15–17]; Lys [13,14,16]; Met [13,14,16]; Pro [13,14,16]; Ser [13,17]; Trp [13,18]; Tyr [13,14]; Val [15]

group of aa-tRNA is bound to (masked by) EFTu·GTP and it is not expected that its nature could influence the process of selection of the cognate tRNA at that stage. In step 2 (proof-reading step) either the peptidyl transferase reaction ( $k_4$ ) takes place or the aminoacylated tRNA dissociates ( $k_{-3}$ ). We assume that a tRNA with a lower stability of its codon-anticodon complex dissociates from the ribosome at a higher speed and therefore has less time (lower probability) to form the peptide bond. However, according to section 3, this sort of tRNA has a more reactive aminoacyl group, which, in turn, compensates for the above-mentioned 'disadvantage'. In other words, we suggest that the composition of codons and the reactivity of the aminoacyl moieties vary in such a way that the ratio  $k_{-3}/k_4$  tends to be similar for different types of tRNA.



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