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Rules governing the genetic code degeneracy/redundancy and spatial organization of the codon informative properties

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The present study is devoted to describing the "logic" implicit in the standard genetic code. Bases are considered as physicochemical entities possessing two essential properties: molecular type and number of Hydrogen bonds involved (bases pairing) in the codon-anticodon specific interactions. It is proposed that the codon structure possesses a dual informative function: on the one hand, it determines its discriminating or non-discriminating character, and on the other hand, it determines a specific amino acid. These two aspects constitute the codon global information. Two different sets of rules are introduced to describe these different phenomena. It is established that, depending on the type of base occupying the second position, only two or three of the six codon properties located at defined positions determine the discriminating or non-discriminating behavior. With regard to the amino acid determining function of the codons for different sets of synonymous (singlets, doublets, triplets, quadruplets, or sextets), the number of informative properties integrating the codon and their typical positions characteristically change. Based on the rules presented here, it can be postulated that a codon can be defined as an asymmetric informative entity, whose global informative capacity results from the spatially organized combination of the six properties assigned by the three bases.

KEYWORDS

genetic code degeneracy, synonymous codons, hydrogen bond, pyrimidine, purine

1 Introduction

The genetic information required for protein synthesis is encoded in specific DNA segments, the so-called protein-coding genes. The genetic information resides on the specific sequence of four nucleotides possessing each of them a distinct nitrogenous base. The specific sequence of bases determines the specific amino acid (AAs) sequences of each protein. The sequence of DNA bases (exons) specifies the sequence of bases of the primary transcript (pre-mRNA). After processing the primary transcript, the sequence of codons (CD), i.e., a set of three adjacent bases of the mRNA determines the amino acid sequence of proteins. The genetic code is a set of rules that ribosome uses to incorporate AA into a protein using the information of the mRNA (1, 2). These rules are the net result of a complex process that involves several steps of specific molecular matching that takes place during the translation of mRNA into proteins: (a) aminoacyl-tRNA synthetases attach an amino acid to the cognate tRNA ("operational code"), (b) the

aminoacyl-tRNA is then used for translation upon binding to mRNA according to (c) the codon-anticodon specific interaction on the ribosome (3–6).

Despite the abundant literature on these molecular interactions, a definitive physical–chemical explanation of the code degeneracy/redundancy is not yet available, and several theoretical models were proposed to explain it. In the present study, these molecular aspects are considered a "black box" and, based on theoretical analyses, explore the possibility of conceiving general formalizations that reliably describe the phenomenon of code degeneracy/redundancy.

The code redundancy refers to the fact that, excluding the 3 stop codons, 61 codons specify 20 amino acids. More specifically, this term refers to the following facts: (a) the anticodon of some tRNA matches more than one codon and (b) some amino acids can be specified by more than one tRNA type having different anticodons (7–11).

The set of codons that specify the same amino acid was classically designed as "synonymous." As a rule, they share the bases located at the first and second positions. Thus, several authors define a codon as the association between a dinucleotide (those located in the first and second positions) and the nucleotide of the third position (3, 12–15). Instead of the term "di-nucleotide," the term "di-base" is used in this study.

The set of four codons corresponding to a particular di-base behaves either as one quadruplet (one set of four synonymous) or as two doublets (two sets composed of two synonymous each) or displays an even more complex behavior that will be later described.

In the present analysis, di-bases are characterized as discriminating (D) or non-discriminating (Non-D). A di-base is defined as discriminating when its corresponding four codons diverge into two doublets depending on the molecular type (pyrimidine or purine) of the base in the third position. A di-base is defined as non-discriminating when its corresponding four codons behave as a quadruplet independently of the base in the third position.

The present study aims to define a set of rules that formally describes the D and Non-D character of the different types of di-bases. This study also attempts to characterize the roles played by different bases in assigning such character to di-bases. Given that bases are considered dual physicochemical entities with two essential properties: (a) molecular type (mT) and (b) the number of Hydrogen bonds (nHb) involved in the codon–anticodon interaction, the rules introduced in this study describe how the combination of four properties of a di-base assign discriminating or non-discriminating character to codons. Finally, the study also introduces rules that describe how different combinations of the six codon properties participate in amino acid specifications.

2 The rules of the genetic code degeneracy/redundancy

This section introduces statements that describe the "logic" implicit in the code degeneracy. These rules can be deduced from classical data about (a) the correspondence between codons and amino acids and (b) the occurrence of redundant codons (1, 2, 16).

2.1 Definitions and nomenclature

In the first part, some classical concepts will be recalled, new terms will be defined, and the relationship between them will be established.

- The codon is the informative unit of the mRNA. It is a sequence of three adjacent bases (B). There are four different bases: uracil (U), cytosine (C), adenine (A), and guanine (G).
- Each codon is denoted by the sequence of three bases (BBB). The base in the first position is denoted as B1 or B– –; in the second position is denoted as B2 or– B –, and in the third position is denoted as B3 or – – B.
- A di-base is denoted as B1B2 or BB–. There are 16 BB–.
- For each di-base BB–, there are four codons given that – –B could be U, C, A, or G.
- A di-base BB– is designated as non-discriminating (Non-D) when the four codons specify a unique amino acid. Then, the four codons of a non-D BB– are synonyms forming a quadruplet.
- A di-base BB– is designated as discriminating (D) when two codons specify a particular amino acid and the other two specify another amino acid. Then, the four codons conform to two groups composed of two synonymous each, i.e., they diverge into two doublets.
- Each base is characterized by two properties: molecular type (mT) and number of H bonds (nHb).
- Two bases, U and C, belong to the pyrimidine type and are denoted as Y. The other two bases, A and G, belong to the purine type and are denoted as R.
- Bases belonging to both molecular types (Y and R) may possess two or three H bonds. This property is denoted as 2 or 3.
- Two bases, U and A, share the property (nHb) 2. The other two, C and G, share the property (nHb) 3.
- Each base may be denoted by indicating its specific pair of properties: Y or R/3 or 2.
- Bases of pyrimidine type are denoted as follows: U is $\frac{Y}{2}$; C is $\frac{Y}{3}$.
- Bases of purine type are denoted as follows: A is $\frac{R}{2}$; G is $\frac{R}{3}$.
- A base is defined as coherent when its properties (Y or R and 3 or 2) coherently contribute to the discriminating or non-discriminating behavior of the di-base BB– they compose.
- A base is defined as non-coherent when its properties (Y or R and 3 or 2) do not contribute coherently to the discriminating or non-discriminating behavior of the di-base BB– they compose. The notions of coherence and non-coherence will be defined in the following paragraphs.
- A CD can be denoted by specifying the six properties of its corresponding three bases.

Example: The CD UGC is denoted as $\frac{Y}{2}\frac{R}{3}\frac{Y}{3}$.

2.2 Rules about the properties molecular type and number of Hydrogen bonds

There are sets of synonymous with different numbers of codons (Figure 1): singlets (unitary set of codons), doublets (set of two synonymous), triplets (set of three synonymous), quadruplets (set of four synonymous), and sextets (set of six synonymous). A triplet can

First Position	Second Position: U	Second Position: C	Second Position: A	Second Position: G	Third Position
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA Stop UAG Stop	UGU Cys UGC Cys UGA Stop UGG Trp	U C A G
C	CUU Leu CUC Leu CUA Leu CUG Leu	CCU Pro CCC Pro CCA Pro CCG Pro	CAU His CAC His CAA Gln CAG Gln	CGU Arg CGC Arg CGA Arg CGG Arg	U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg AGG Arg	U C A G
G	GUU Val GUC Val GUA Val GUG Val	GCU Ala GCC Ala GCA Ala GCG Ala	GAU Asp GAC Asp GAA Glu GAG Glu	GGU Gly GGC Gly GGA Gly GGG Gly	U C A G

FIGURE 1
The genetic code. The table illustrates the sets of codons that specify each amino acid.

be considered as an association between a doublet and a singlet, and a sextet can be considered as an association between a quadruplet and a doublet.

To make the analysis easier, the four codons corresponding to each BB– will be considered as if they were just quadruplets or doublets. There are, however, two special cases (AU– and UG–) that do not exactly adjust to this definition. As a first approach, these BB– will be considered as being discriminating. In this way, in the simplest diagram (Figure 2), each of the 16 BB– is represented as being discriminating or non-discriminating. In the following sections, the details concerning the special cases for the standard genetic code will be considered step by step, from the simplest picture to the most complex one, and the rules of increasing complexity will then be introduced.

2.2.1 The role of bases: adenine and cytosine

With regard to considering the bases A and C, it is shown in Figure 2 as follows:

Rule 1. BB–which includes C are non-discriminating except when B2 is A and BB– which contain A are discriminating except when B2 is C.

This rule reveals three essential facts which are as follows:

(1) C assigns a non-D behavior to di-bases. C possesses a non-D characteristic.

(2) A assigns a D behavior to di-bases. A possesses a D characteristic.

Note that BB–, composed of combinations of A and C, such as CA– and AC–, consists of combinations of bases with opposing characteristics. This opposition of characteristics is solved in a way indicating that B1 and B2 (the first and the second positions) display different informative roles.

(3) B2, the second position, has a relevant informative value. In considering those BB– that are combinations of C and A, the discriminating or non-discriminating behavior is determined by B2, i.e., it depends on the characteristic of the base located in the second position.

2.2.2 The role of bases: uracil and guanine

There is no equivalent rule applicable to bases U and G. It will be explained later that these bases are different from A and C with respect to a characteristic defined as coherence.

Regarding BB–, composed of combinations of U and G (a) codons containing the combination GU– converge into a quadruplet, and (b) codons containing the combination UG– diverge into two doublets.

These facts imply that.

(1) The structure –U– assigns a non-D behavior to di-bases. U possesses a non-D characteristic;

(2) The structure –G– assigns a D behavior to di-bases. G possesses a D characteristic.

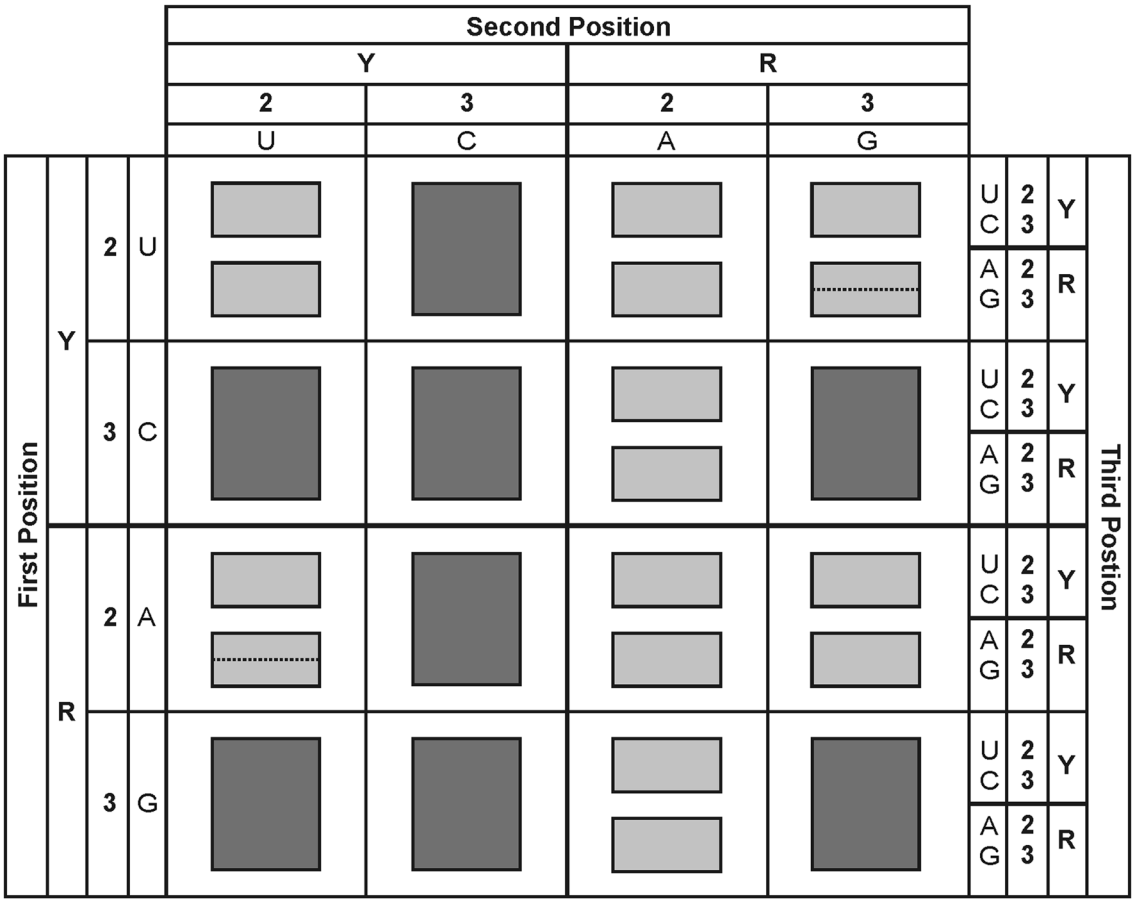


FIGURE 2
Simplified picture of the genetic code degeneracy. The four codons of each BB are represented as if they were only quadruplets or doublets. Dark gray: quadruplets. Light gray: doublets. Dotted lines indicate special cases of doublets divergence into two singlets. The distribution of the properties Y, R, 2, and 3 is indicated.

2.2.3 The role of the property molecular type (Y, R)

Taking into account that C and U share the property Y and that A and G share the property R, from the previous paragraphs can be enunciated another general rule:

Rule 2. Y is a non-discriminating property, and R is a discriminating property.

2.2.4 The role of the property nHb (2, 3)

C and G are characterized by property 3 and U and A are characterized by property 2. Analyzing the distribution of quadruplets and doublets in connection with properties 2 and 3 (Figure 2), another general rule can be postulated:

Rule 3. BB–whose bases have the property 3 are non-discriminating and BB–whose bases have the property 2 are discriminating.

A more general enunciation of this rule is as follows:

Rule 4. Three (3) is a non-discriminating property, and 2 is a discriminating property

All these statements are included in the following rule:

$--\frac{Y}{}--$ converge into quadruplets except $-\frac{Y}{2}\frac{}{2}-$ and $--\frac{R}{}--$ diverge into doublets except $-\frac{R}{3}\frac{}{3.}-$

2.3 Toward more general rules

The following paragraphs introduce two sets of rules to describe that the codon structure possesses a dual informative function: on the one hand, it determines (a) the discriminating or non-discriminating character, and on the other hand, it determines (b) a specific amino acid. These rules reveal the significance of the spatial position, i.e., the spatial organization, of the properties Y, R, 3, and 2.

2.3.1 The rules of determination of the discriminating or non-discriminating character of the BB–(quadruplets vs. doublets)

The behavior described by Rule 1 is due to the fact that (a) base C is characterized by the coincidence of two non-discriminating

properties (Y and 3), and (b) base A is defined by the coincidence of two discriminating properties (R and 2). These conditions are defined as coherence. C and A are coherent bases.

Bases U and G do not fulfill this condition. Base U possesses a discriminating property associated with a non-discriminating one (2 and Y, respectively), while G is characterized by the association of a non-discriminating with a discriminating property (3 and R, respectively). We define this condition as non-coherence. U and G are non-coherent bases.

The relevance of the spatial position is revealed by the fact that all the rules previously enunciated can be integrated into a unique statement:

First Law: Three properties located at defined positions determine the discriminating or non-discriminating character of a BB–.

The specific positions of these three properties within the codon structure can be indicated as follows:

$$\frac{\quad}{nHb_{3-2}}\frac{mT_{Y-R}}{nHB_{3-2}}-$$

The other three properties of the codon are irrelevant, and they do not possess informative value in this respect.

Second Law: BB– are discriminating or non-discriminating when two of these properties are so.

A derivation of the second law dictates that

A coherent B2 determines by itself the D or non-D characteristic of di-bases.

From this, two additional enunciations are derived as follows:

$-\frac{Y}{3}-$ is non-discriminating BB–, and their four CDs converge into quadruplets, and $-\frac{R}{2}-$ are discriminating BB–, their four CDs diverge into doublets.

In these two conditions, the remaining four properties are informatively irrelevant.

Another corollary of the first law establishes that

In BB–, with non-coherent B2, the discriminating or non-discriminating characteristic also depends on the property nHb of B1.

2.3.2 Rules about the amino acid-specifying information of the codon

There are BB– whose four codons converge into quadruplets and they specify a single amino acid.

There are BB– whose four codons diverge into doublets that specify two different amino acids.

There are BB– whose four codons diverge into one doublet and two singlets. In some cases, the doublet + one singlet conform a triplet that specifies a single amino acid while the other singlet specify a different amino acid. In other cases, the singlets correspond to the Start or Stop codon.

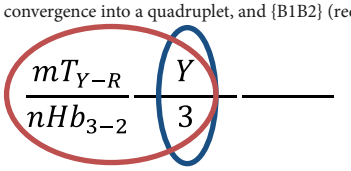
The following paragraphs show that for each of the above-mentioned conditions, there are different rules describing how a codon specifies a particular amino acid. These rules describe that the "quantity" of information, i.e., the number of informative properties, required for the specification of an amino acid by quadruplets, doublets, and singlets significantly differs. Only when an amino acid is specified by a singlet, the complete set of informative properties of the codon is required.

2.3.2.1 The rule of the specification of amino acids by quadruplets

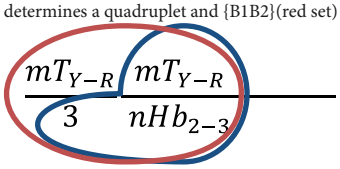
First rule: Four of the six properties of the CD are required to specify an AA by quadruplets.

1. In non-discriminating BB– the amino acid specification depends on B2 + B1

1.1. In non-discriminating BB– with coherent B2, $\{\frac{Y}{3}\}$(blue set) determines the convergence into a quadruplet, and {B1B2} (red set) specifies the AA



1.2. In non-discriminating BB– with non-coherent B2, $\{\frac{-}{3}$ in B1 + B2$\}$(blue set) determines a quadruplet and {B1B2}(red set) specifies the AA

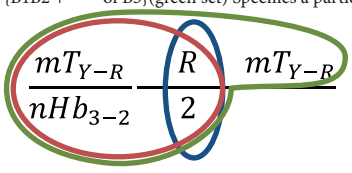


2.3.2.2 The rule of the specification of amino acids by doublets

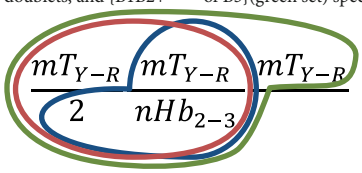
Second rule: Five of the six properties of a CD are required to specify an AA by doublets.

2. In discriminating BB–, the amino acid specification also depends on the property mT ($\frac{Y}{-}$ vs. $\frac{R}{-}$) of B3.

2.1. In discriminating BB– With coherent B2, $\{\frac{R}{2}\}$(blue set) determines the divergence into two doublets, {B1B2}(red set) Specifies which pair of doublets, and {B1B2 + $\frac{mT}{-}$ of B3}(green set) Specifies a particular AA



2.2. In discriminating BB– with non-coherent B2, {$\frac{-}{2}$ in B1 + B2}(blue set) determines the divergence in two doublets, {B1B2}(red set) specifies which pair of doublets, and {B1B2+ $\frac{mT}{}$ of B3}(green set) specifies a particular AA

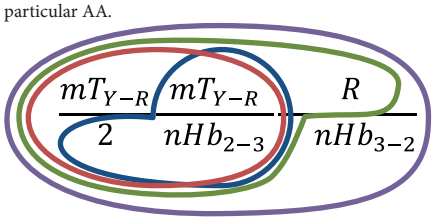


2.3.2.3 The rule of amino acid specification by singlets

Third rule: The six properties of a CD are needed for the specification of AA by singlets.

The specification of an amino acid by singlets can be considered special cases in which doublets diverge into two singlets. This condition requires using the six properties of the codon and takes place only when a discriminating BB– possesses a non-coherent B2 and $\frac{R}{}$ in B3. In these cases, the amino acid specification depends also on the property nHb ($\frac{}{2\ vs\ 3}$) of B3.

Only discriminating BB– with non-coherent B2 and $\frac{R}{}$ in B3 can diverge into singlets: {$\frac{-}{2}$ in B1 + B2}(blue set) determines the discriminating characteristic, {B1B2}(red set) identifies a particular BB, {B1B2+ $\frac{R}{}$ in B3}(green set) allows the divergence into singlets, and {B1B2+ $\frac{R}{}$ in B3+ $\frac{}{2\ vs\ 3}$ in B3}(violet set) specifies a particular AA.



2.3.2.4 The hierarchy of the informative properties of the codon as revealed by a tree structure

A tree structure was already used to analyze the syntactic structure of the genetic code and investigate the relationship between the codon tree and the hierarchy of the amino acid categorizations (17–19). In this study, a tree structure was used to represent the hierarchy of the properties mT and nHb in relation to their position within the codon, in the determination of the discriminating or non-discriminating character of di-bases and in the specification of amino acids (Figure 3).

The induction algorithm ID3 (20) was implemented in order to classify the 64 codons into 21 classes (20 amino acids and stop codons). The six properties of codons were used as attributes.

The *height* of the tree is determined by the six properties of the three bases. Each node can be thought of as the answer to a question: Is the property discriminating or non-discriminating? With regard to the bifurcation at each node, the branch directed to the right corresponds to non-discriminating and that directed to the left corresponds to discriminating. When all the branches originated at a definite node (a subtree) correspond to the same amino acid, the subtree is replaced by a terminal or "leaf" node. The "morphology" of the tree depends on the order in which the six codon properties are organized in successive nodes.

According to the algorithm, the information gain, i.e., the relative importance of the attributes is expressed by the series: nHb of B2 > mT of B2 > nHb of B1 = mT of B1 > mT of B3 > nHb of B3. Among the different possible trees that maximize information gain, Figure 3 represents one in which the properties of the bases were arranged according to the following decreasing hierarchy: nHb of B2 > mT of B2 > nHb of B1 > mT of B1 > mT of B3 > nHb of B3. This hierarchical order was chosen because it coincided with that expected from the sets of rules introduced in this study. The hierarchy of the different properties depends on their positions within the codon: the maximal hierarchy (the root node) corresponds to the properties of the second position (nHb = mT), the following hierarchy corresponds to the first position (nHb > mT), and the last hierarchy corresponds to the third position (mT > nHb). The tree graphically shows that four, five, and six nodes, i.e., codon properties, are required to specify quadruplets, doublets, and singlets, respectively. It can be noted that this tree reliably reproduces the three rules about amino acid specification described under the title, 2.3.2 Rules about the amino acid-specifying information of the codon.

3 Discussion and concluding remarks

The relevance of nucleotide positions within the codon was proposed and exhaustively analyzed from different perspectives since many years ago. As early as 1960–70, Woese (21, 22) proposed that the origin of a codon assignment, i.e., specification of related amino acids, could have depended on a primitive translation process in which groups of chemically related codons could specify groups of chemically related amino acids, a hypothesis, based on direct physicochemical interactions between nucleic acids and amino acids that was named as "group codon assignments." In 1966, F. Crick (23) proposed that the interaction between the nucleotide of the 5'end of the anticodon and that of the 3'position of the codon does not respond to the classical base pairing rules, a phenomenon known as the "wobble" hypothesis. Later, Lagerkvist (16, 24) observed that the intensity of the pairing force of the nucleotides located at the first two positions and the purine/pyrimidine nature of the base of the second position are relevant criteria for the categorization of codons into two families of degeneracy. It is interesting that other authors also considered the properties of mT and nHb of bases as criteria for the construction of Boolean algebraic models of degeneracy (25, 26). More recent models of code degeneracy assigned significant importance to the architecture of the anticodon loop of the tRNA and the molecular organization of the ribosome-decoding center (4). Analyses based on cryogenic electron microscopy also highlight the role of the ribosome in establishing the degeneracy (27).

The role of the nHb was also highlighted by Danckwerts and Neubert (28), who showed that when the sum of the nHb in B1B2– is 6, they converge into a quadruplet; however, when the sum is 4, they diverge into doublets. Konjevoda and Štambuk (29) show that when the sum is 5, the mT of B2 defines whether the di-base forms quadruplets or doublets.

Some research works that study the code degeneracy from an evolutionary perspective have attempted to elucidate the possible

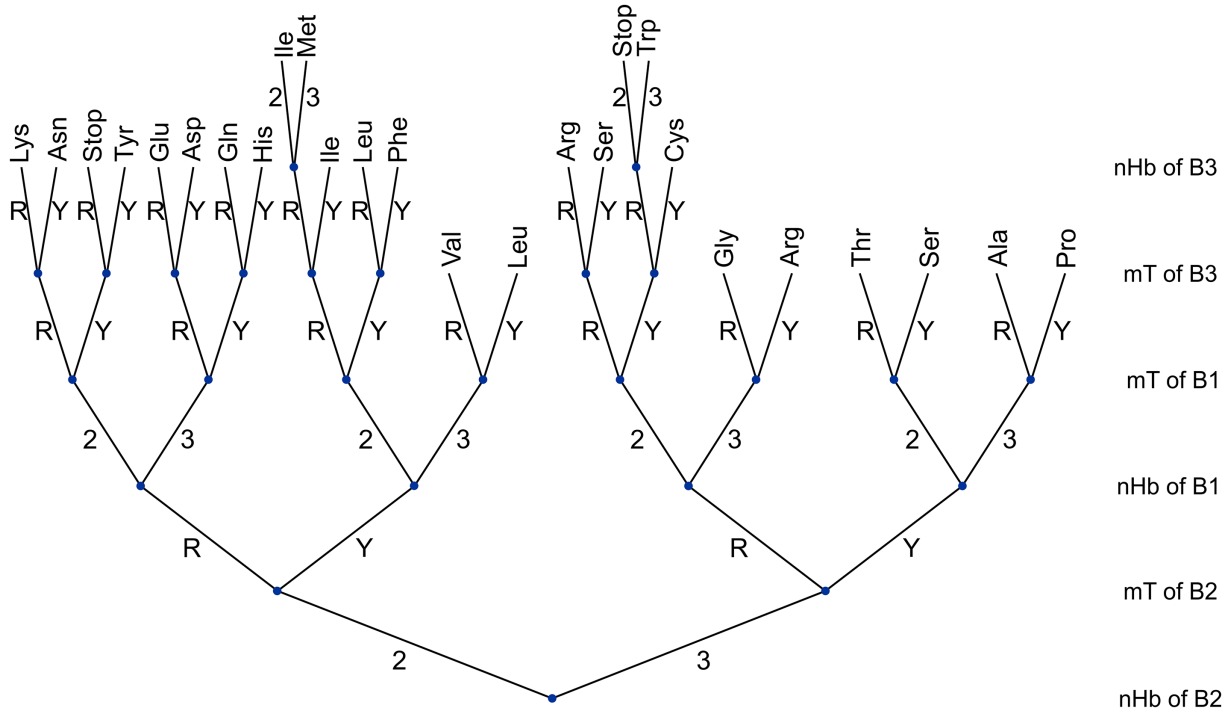


FIGURE 3
A tree representing the specification of amino acids in terms of the essential properties of the bases.

origin and evolution of the genetic code, in the context of the biology of primitive organisms (protocells), considering two aspects: (a) direct stereochemical interactions between codons and amino acids and (b) the biosynthetic pathways of various amino acids' synthesis (30–35). Some of these studies were devoted to studying these interactions through molecular dynamics simulations in order to analyze the forces acting between adjacent atoms (36, 37). Other evolutionary analyses have focused on the role natural selection could have played in shaping a robust code, minimizing the impact of mutations and mistranslation on protein structure and function (38–42). This phenomenon is closely associated with codon usage (43–45). The relational model of the structure of the standard genetic code analyzed by Konjevoda and Štambuk (29) is a valuable attempt to unify these and other evolving studies. Other authors emphasize the role of tRNA in the origin and evolution of the genetic code, highlighting the interactions between aminoacyl-tRNA synthetases and different tRNA domains, an operational code of tRNA aminoacylation and a standard tRNA code composed of 46 anticodons (46–52).

The set of rules introduced in this study considers a codon as an entity with a double function. The spatial organization of the six attributes of codons informs about two related, but essentially different, phenomena. Apart from determining a specific amino acid, there is a "logic" that associates the codon composition with its discriminating or non-discriminating character. These two aspects constitute the global information of the codon, and two different sets of rules are needed to describe these different phenomena.

These rules establish that, depending on the type of base (coherent or non-coherent) occupying the second position, only two or three of the six codon properties located at defined positions determine the discriminating or non-discriminating behavior. In addition, the number of properties and also their positions characteristically change when an amino acid is specified by different sized sets of synonymous codons (quadruplets, doublets, and singlets).

It is clear that the second position possesses a relevant function: a coherent B2 *per se* determines the discriminating or non-discriminating character of codons. However, in the case of codons with non-coherent B2, additional information is required to specify the discriminating vs. non-discriminating character. In considering a codon with a non-coherent B2, the other properties possess different roles depending on their location at B1 or B3: (a) the property nHb of B1 is needed to determine the discriminating vs. non-discriminating character. Thus, the property 2 allows the divergence into two doublets. In this case, the property mT of B1 does not have an informative value; (b) on the other hand, the property mT of B3 is needed to allow the divergence into singlets. In fact, R in B3 allows the divergence while Y does not. Conversely, the property nHb of B3 does not have such an informative value.

On these bases, the present study reinforces the idea that a codon is an asymmetrically organized informative entity since the same informative elements possess different informative roles when they are in different positions, i.e., B1 or B3, with respect to a non-coherent B2.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

MR: Conceptualization, Formal analysis, Methodology, Writing – review & editing. RK: Conceptualization, Formal analysis, Writing – original draft. VF: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – review & editing.

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