A Mathematical Model Accounting for the Organisation in Multiplets of the Genetic Code

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Abstract

Requiring stability of genetic code against translation errors, modelised by suitable mathematical operators in the crystal basis model of the genetic code, the main features of the organisation in multiplets of the mitochondrial and of the standard genetic code are explained.

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1 Introduction

As it is well known, the DNA macromolecule is constituted by two linear chains of nucleotides in a double helix shape. There are four different nucleotides, characterized by their bases: adenine (A) and guanine (G) deriving from purine, and cytosine (C) and thymine (T) coming from pyrimidine, T being replaced by uracile (U) in RNA. The genetic information is transmitted via the messenger ribonucleic acid or mRNA. During this operation, called transcription, the A, G, C, T bases in the DNA are associated respectively to the U, C, G, A bases. Through a complicated biochemical process, a triple of nucleotides or codon will be related to an amino-acid. More precisely, a codon is defined as an ordered sequence of three nucleotides, therefore there are $4^3 = 64$ different codons. Only 20 different amino-acids appear in the peptide chains which form the proteins. We list them with the standard abbreviation: Alanine (Ala), Arginine (Arg), Asparagine (Asn), Aspartic acid (Asp), Cysteine (Cys), Glutamine (Gln), Glutamic acid (Glu), Glycine (Gly), Histidine (His), Isoleucine (Ile), Leucine (Leu), Lysine (Lys), Methionine (Met), Phenylalanine (Phe), Proline (Pro), Serine (Ser), Threonine (Thr), Tryptophane (Trp), Tyrosine (Tyr), Valine (Val). It follows that the genetic code, i.e. the association between codons and amino-acids, is degenerated. In the vertebrate mitochondrial code (VMC) (see Table [1]) 60 of such triples are connected to 20 the amino-acids, the remaining 4 codons, called nonsense or stop-codons and denoted by the symbol Ter, playing the role to stop the biosynthesis.

Since the discovery of the genetic code [1], a couple of very puzzling questions have arisen: why only twenty amino acids (a.a.) are used in nature to build up proteins? why the genetic code has a peculiar structure in multiplets ranging from sextets to singlets, in particular: for VMC 2 sextets, 7 quartets and 12 doublets; for the eukaryotic or standard genetic code 3 sextets, 5 quartets, 2 triplets, 9 doublets and 2 singlets? An attempt to explain the existence of only 20 amino acids is given by the hypothesis that originally the quantum of coding information was transmitted by a pair of nucleotides instead that by the present triple of nucleotides (codon) and $4 \times 4 = 16$ is a number close to 20. However this explanation is in contradiction with other hypothesis on the structure of the primordial code (quadruplets of nucleotides or a subset of the present 64 triples). Other explanations are based on correspondence between the properties of the amino acids and the structure of the corresponding codons. Although it seems now clear that a correspondence of this kind exists and it can explain why some amino acids are encoded by more codons than others, it is not evident how the interplay between a.a. and codons leads to the existing multiplets structure. A strong and probably correct argument makes appeal to stability considerations, i.e. to state that the the genetic code has remained unchanged over a vast time period because it has adopted the most appropriate organisation to oppose the most frequent and lethal changes. However no consistent model, at my knowledge, has been proposed to explain the actual multiplets structure in the light of the above statement. It is known that the translation errors are the main source of devastating effect in the construction of the polypeptide chains. Errors in reading the nucleotide in 3rd position are more frequent than errors in reading the nucleotide in 1st position and the latter are more frequent than those

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1 The literature on the genetic code is extremely large. For a recent review with a wide selection of references to the original papers see [1]
in 2nd or central position. Clearly a protection against the translation errors represented by transitions, i.e. the replacement by a pyrimidine (purine) by the other pyrimidine (purine), which are the most common mutations, is obtained by encoding the same a.a. by codons of the form XZY or XZR. In the following the standard notation is used:

\[ X, Z, N = C, U, G, A \quad Y = C, U \quad R = G, A \]  

(1)

Codons encoding the same a.a., i.e. belonging to the same multiplet are called synonymous. Similarly a.a. encoded by codons of the form XZN are, in some way, protected by the effects of the translation errors represented by tranversions (pyrimidine into purine or viceversa). But why there are only six or five quartets? why do only two or three sextets appear? why the quartets and sextets have the structure they have for the first two nucleotides XZ? The complete stability against reading errors is in obvious conflict with the advantage to encode many a.a., so to allow a very large variety of byosynthesis products. It is the aim of this paper to propose a mathematical model which may explain both the number of the natural amino acids and the structure in multiplets. The framework in which the model is proposed is the crystal basis model of the genetic code \[ \text{[2]} \] in which the 4 nucleotides are assigned to the 4-dim irreducible fundamental representation (irreps.) \( (1/2, 1/2) \) of \( U_{q=0}(sl(2) \oplus sl(2)) \) with the following assignment for the values of the third component of \( \vec{J} \) for the two \( sl(2) \) which in the following will be denoted as \( sl_H(2) \) and \( sl_V(2) \) :

\[ \begin{align*}
C & \equiv (+1/2, +1/2) \\
T/U & \equiv (-1/2, +1/2) \\
G & \equiv (+1/2, -1/2) \\
A & \equiv (-1/2, -1/2)
\end{align*} \]  

(2)

and the codons, triple of nucleotides, to the 3-fold tensor product of \( (1/2, 1/2) \). We report in Table 1 the assignment of the codons to the different irreps. and the correspondence with the encoded a.a. in the vertebral mitochondrial (VMC) and in the standard universal genetic code (SUC). Let us emphasize that the assignments of the codons to the different irreps. is a straightforward consequence of the assumed behaviour of the nucleotides eq.(2) and of the theorem on the tensor product of irreps. in the crystal basis \[ \text{[3]} \]. The idea of this work is to mathematically represent the effects of translation errors by suitable crystal tensor operator \[ \text{[4]} \]. Imposing stability of the genetic code with respect to these errors, i.e. that codons which are most sensitive to be read in a wrong way correspond to synonymous codons in the encoding process, we find the main features of the multiplet structure of the VMC, which is believed to represent a primordial form of the code, and of SUC. The paper is organised as it follows: in Sec. 2 the general ideas of modelisation of misreading of codons are introduced; in Sec. 3 a detailed discussion of the consequences of the mathematical modelisation is given. Indeed in order to study the dependence of the results from the assumptions of the operators mimicking the translational errors, two mathematical schemes are analysed, discussing which results are model dependent. In Sec. 4 a critical discussion of the obtained results as well as some directions for further developments are presented.
2 Modelisation of misreading of codons

We assume, on phenomenogical grounds, that there is a hierarchy in the occurrence of translation errors and, in order of decreasing intensity, we consider:

1. the transitions, in particular $C \rightarrow U$ or $G \rightarrow A$, concerning nucleotides in the 3rd position
2. the tranversions, in particular $C \rightarrow G$, $U \rightarrow A$ and $C \rightarrow A$, in the nucleotides in 3rd position.
3. the transitions (resp. tranversions) concerning nucleotides in 1st position
4. the transitions (resp. tranversions) concerning nucleotides in 2nd position
5. the mutation induced by the transitions (resp. tranversions) on the first two nucleotides

Transitions (tranversions) of the nucleotide in the middle position will be considered far weaker than transitions (tranversions) in other positions both on phenomenogical grounds and on the argument that, in the spirit of the hierarchical structure of the intensity of mutations, the change of the other nucleotides is preferred. Indeed there are phenomenogical arguments, confirmed also by our model, that these changes can be neglected. However we prefer to discuss the translational errors in the above order as it allows the most natural introduction of the mathematical structure of the operators modelising the errors. The hierarchy in the translation errors mechanisms means that a multiplet formed in a level is frozen; in the subsequent levels, the merging of two whole multiplets in a larger structure is possible, if it is induced by the relevant tensor operator. If the transition is allowed only for some member of a multiplet, there is conflict between the choice of merging the multiplet in a larger one, so decreasing the variety of encoded a.a. but increasing the protection or preserving the multiplets decreasing the level of protection. In this case, the formation of larger structures will generally take place or not according to the rule to protect the weakest codons, i.e. the codons more inclined to be misread. We assume that misreading of nucleotide C or A is the most common. However in the following we shall discuss in some detail each of these case. Let us emphasize that we want to build the most simple model in which the codons, which are most subject to reading errors, are synonymous; in this spirit the explicitly analysed transitions ($C \rightarrow U$, $G \rightarrow A$) or transversions ($C \rightarrow G$, $U \rightarrow A$, $C \rightarrow A$) have not to be considered as the only possible changes, but as the representatives which allow the most simple modelisation. In other words transitions and transversions in the reversed directions happen, but the protection against their effects is assured once the concerned codons belong to the same multiplet. We consider only the transversions decreasing or leaving unchanged the value of $J_{H,3}$. The tranversion $U \rightarrow G$ implies the increasing of one unity of $J_{H,3}$, therefore it is not explicitly considered. This is an essentially irrelevant simplification, because it is possible to show that a suitable modelisation of this transversion leave the obtained results unmodified.

In the following we recall briefly the main properties of the $(q \rightarrow 0)$-tensor operators or crystal tensor operators, for a generic $U_{q \rightarrow 0}(sl(2))$. They transform as

$$J_3(\tau_m^j) \equiv m\tau_m^j \quad J_\pm(\tau_m^j) \equiv \tau_m^{j \pm 1}$$

(3)
Clearly, if $|m| > j$ then $\tau^j_m$ has to be considered vanishing. The state $\psi_{j_1 m_1}$ will be connected by the $(q \to 0)$-tensor operator $\tau^j_m$ to the state $\psi_{J M}$ by the $(q \to 0)$-Wigner-Eckart theorem if

$$\psi_{J M} = \psi_{j_1 m_1} \otimes \psi_{jm}$$

(4)

A peculiar feature of the Wigner-Eckart theorem, in the limit $q \to 0$, is that the selection rules do depend not only on the rank of the tensor operator and on the initial state, but in a crucial way from the specific component of the tensor in consideration. The states $\psi_{J M}$ can be explicitly computed, up to irrelevant numerical factors, by performing the tensor product, according to the rules given in [3], of irreps. $j_1$ and $j$. The tensor product of two irreducible representations in the crystal basis is not commutative, therefore one has to specify which is the first representation in the product. A final important remark: it is clear from the Table 1 that there are generally more than one irrep. labelled by the same value of $(J_H, J_V)$ whose content in the constituent nucleotides is different. The transformation properties of a crystal tensor operator determine which state is related to an initial one, only according to the irrep. to which the initial state belongs, therefore the mathematical modelisation by means of an unique tensor operator is expected to be too simple and inadequate. Indeed the nucleotides are molecules with very different physical-chemical properties, while in the crystal basis model they all are handled on the same basis as vectors of an irreducible module. Moreover it can be expected that some reading errors of a nucleotide depend also from the nature of the neighbouring nucleotides. In the following we shall take in some way into account this fact by a suitable choice of the nature of the tensor operator. Notwithstanding these simplifications of the mathematical modelisation, it is quite amazing how many features of the organisation of the genetic code can be obtained. Note that, in order not to overload the notation, we do not explicitly specify the action of the operators on the nucleotides, but only their transformation properties under $U_{q \to 0}(sl_H(2) \oplus sl_V(2))$. Hopefully it will be clear from the context which kind of process we are considering.

3 Mathematical schemes

We model the transitions and the transversions by the following crystal tensor operator, the value of the component being determined by the labels of the nucleotides, see eq.(2):

$$C \to U \quad \text{or} \quad G \to A \quad \tau^1_{H,-1} \otimes \tau^a_{V,0}$$

(5)

$$C \to G \quad \text{or} \quad U \to A \quad \tau^b_{H,0} \otimes \tau^1_{V,-1}$$

(6)

$$C \to A \quad \tau^c_{H,-1} \otimes \tau^d_{V,-1}$$

(7)

where the values of $a$, $b$, $c$ and $d$ depend on the position inside the codons of the misread nucleotide and on the irreps. to which the codons belong, see below. The above choice for the horizontal (resp. vertical) part of the crystal vector operator in eq.(5) (reps. eq.(6)) is indeed the most simple choice according to the change in the labels of the states of codons for transitions (resp. transversions). The choice of the rank of the vertical (resp. horizontal) part of the crystal operator in eq.(5) (resp. eq.(6)), as well as the tensor operator modelling
the transversion $C \rightarrow A$, is someway arbitrary. It is indeed a way of taking into account, in mathematical language, the chemical difference between the nucleotides and the difference in the mechanism responsible for misreading nucleotides in different positions inside the codons. The value of the rank of the operator modelising the translational errors in 2nd position will be generally assumed larger than the one describing errors in 1st position and the latter one will be generally assumed larger than the one describing errors in 3rd position, so to model the less frequent misreading. In particular, in the scheme we shall discuss more in detail, for the transitions the rank $a$ of the ”vertical” tensor operator $\tau^a_{V,0}$ will be assumed to be 0, 1, 2 respectively for transitions in 3rd, 1st and 2nd position. In the tensor product with the state the crystal operator $\tau_\alpha (\alpha = H, V)$ will be considered in the second position. A codon, e.g. XZN, will be considered subject to a translational error, e.g. to be read as XZN', if the crystal operator modelising the relevant translational error will connect, in the sense above explained, the state $\psi(XZN)$ with the state $\psi(XZN')$ where $\psi(XZN)$ is the state in the irreps. of $U_{q \rightarrow 0}(sl_H(2) \oplus sl_V(2))$, see Table 1, specifying the codon XZN.

### 3.1 Substitution of 3rd nucleotide

To study the transitions in 3rd position in the codons XZC and XZG, where X and Z are any nucleotide, we consider the action of the operator given by eq.(5) with $a = 0$ on the corresponding states: (in the following the equations have to be read by the western rule from left to right)

\[
\psi(XZC) \circ (\tau^0_{H,-1} \otimes \tau^0_{V,0}) \implies \psi(XZU) \tag{8}
\]
\[
\psi(XZG) \circ (\tau^0_{H,-1} \otimes \tau^0_{V,0}) \implies \psi(XZA) \tag{9}
\]

We impose the codons XZC (resp. XZG) and XZU (resp. XZA) to be synonymous, if the states are connected by the $\tau^1_{H,-1} \otimes \tau^0_{V,0}$ according to the $(q \rightarrow 0)$-Wigner-Eckart theorem. We get the splitting of the 64 codons in 32 doublets of the form XZR and XZY. Remark that the final pattern is unchanged if in eq.(8) we replace $\tau^0_{V,0}$ by $\tau^1_{V,0}$. To study the tranversions in 3rd position in the codons XZC and XZU we consider the action of the crystal operators given by eq.(3) and eq.(7) on the corresponding states:

\[
\psi(XZC) \circ (\tau^b_{H,0} \otimes \tau^1_{V,-1}) \implies \psi(XZG) \tag{10}
\]
\[
\psi(XZU) \circ (\tau^b_{H,0} \otimes \tau^1_{V,-1}) \implies \psi(XZA) \tag{11}
\]
\[
\psi(XZC) \circ (\tau^b_{H,-1} \otimes \tau^1_{V,-1}) \implies \psi(XZA) \tag{12}
\]

where in eqs.(10),(11),(12) $b = 2$ if the dinucleotide XZ, i.e. the state formed by the first two nucleotides in the initial codon, belongs to an irrep. with $J_V = 0$ or is a state with lowest weight for slV(2) or for slH(2), if $J_H \neq 0$, see Table 2 (i.e. when the first two nucleotides are: CA, GA, CG, UG, UA, UU, AU, AA, GG, AG) and $b = 1$ otherwise. We have previously given arguments to motivate the introduction of different tensor operators to describe the misreading of the same nucleotide in different codons, it is just a simple way of mathematically mimicking the dependence of the translational errors or misreading from the
neighbouring nucleotides. For the transitions, which imply errors in the translation between members of the same chemical family, the tensor operators depend only from the position in the codons of the misread nucleotide. Let us comment more on the mathematical meaning of our assumptions. Due to the peculiar properties of the crystal basis the tensor operators can be assumed to consist of a part, let us say $\eta$, with definite transformations properties with respect to the generators of $U_{q=0}(sl(2) \oplus sl(2))$ acting on the first two nucleotides and of a part, let us say $\tau$, with definite transformations properties with respect to the generators of $U_{q=0}(sl(2) \oplus sl(2))$ acting on the whole codon. Under the action of $\eta$ the state of initial codon changes into a "virtual" state transformed by $\tau$ into a final state. If the labels of the final state correspond to the labels of the state describing the codon, the transversion is induced, otherwise it is not allowed, i.e. there is no misreading. This kind of reasoning is applied in the case of substitution of two nucleotides, see Subsection 3.4. The choice of a different rank of $\tau_{H,0}^b$ in eqs., (10), (11), (12) is a simple way to take into account this complex mechanism. One may reformulate the above conditions as it follows: in eqs,(10),(11) $b = 2$ if the codon and the one obtained by transversion belong to the same irrep. or if the initial codon belongs to an irrep. with $J_H = \frac{3}{2}$ and $b = 1$ otherwise; in eq.(12) $b = 2$, if the codons XZC and XZU belong to the same irrep. and $b = 1$ otherwise. These conditions are simpler, but the dependence of the rank of the operators also from the irrep. of the final codon may sound unsatisfactory. It turns out that:

- eq.(10) forbids transversions UUC $\rightarrow$ UUG, AUC $\rightarrow$ AUG, AAC $\rightarrow$ AAG, UAC $\rightarrow$ UAG, GAC $\rightarrow$ GAG, and CAC $\rightarrow$ CAG;

- eq.(11) forbids transversions UUU $\rightarrow$ UUA, AUU $\rightarrow$ AUA, AAU $\rightarrow$ AAA, UAU $\rightarrow$ UAA, AGU $\rightarrow$ AGA, GAU $\rightarrow$ GAA, UGU $\rightarrow$ UGA and CAU $\rightarrow$ CAA;

- eq.(12) forbids transversions UUC $\rightarrow$ UUA, AUC $\rightarrow$ AUA, AAC $\rightarrow$ AAA, UAC $\rightarrow$ UAA, AGC $\rightarrow$ AGA, GAC $\rightarrow$ GAA, UGC $\rightarrow$ UGA and CAC $\rightarrow$ CAA.

Therefore we obtain the merging of 16 doublets in 8 quartets, the quartets being the codons whose the first two nucleotides are: CC, CU, CG, UC, GG, GC, GU, and AC. Let us note that the transitions AGC $\rightarrow$ AGG and UGC $\rightarrow$ UGG are allowed; a way of insuring protection without decreasing the number of amino acids encoded is to make an appropriate choice for the codons AGG and UGG in the encoding process; indeed in VMC the first is a stop codon while the second encodes for a a very rare amino acid Trp. At this stage the assignment of the codons, differing for the 3rd nucleotide, to different multiplets is decided. The next steps can produce the joining of doublets and quartets in quartets or sextets or in, a priori, octets.

Let us study what it is obtained if we change the mathematical modelisation of the direct transversions (C $\rightarrow$ G, U $\rightarrow$ A) in 3rd position using the following operator

$$\psi(XZC) \circ (\tau_{H,0}^b \otimes \tau_{V,-1}^1) \implies \psi(XZG)$$

$$\psi(XZU) \circ (\tau_{H,0}^b \otimes \tau_{V,-1}^1) \implies \psi(XZA)$$

where:
• $\alpha = 2$ if the state $\phi(XZ)$ of the dinucleotide $XZ$ is a lowest weight state for $sl_H(2)$ in an irrep. with $J_H \neq 0$ (i.e. from Table 2: $XZ = UU, AU, AA$) and $\alpha = 1$ otherwise.

• $\beta = 0$, if the dinucleotide is a state unmodified by the action of a vector operator $\eta_{V,O}$ acting on it, in the sense that the labels of the state

$$\phi'(XZ) = \phi(XZ) \circ \eta_{V,O}$$

are the same than the state $\phi(XZ)$, and $\beta = 1$ otherwise, i.e. from Table 2: $XZ = CU, GU, CC, UC, UU, GC, AC, AU$.

In the spirit of the hierarchical strength of misreading errors, a quartet will be formed surely if both the codons $XZR$ are transformed in $XZY$. It turns out the merging of 16 doublets in 8 quartets, the quartets being the codons whose the first two nucleotides are: CC, CU, CG, UC, GG, GC, GU, and AC. It turns out also that:

• in AGC, URC, CAC and GAC the nucleotide C in 3rd position can be transformed in G while in AGU and UGU the nucleotide U in 3rd position cannot be transformed in A

• in UUU and AUU the U in the end position can be transformed in A, while in UUC and AUC the C cannot be transformed in U.

Let us analyse more in detail the function and physical-chemical properties of the doublets in which only one state is subject to misreading. We remark that UAY and AGY encode in VMC the stop codons. Moreover the the physical-chemical properties of His (encoded by CAY), Asp (GAY), Cys (UGY) and Asn (AAY) are, respectively, close to the properties of Gln (CAR), Glu (GAR), Trp (UGR) and Lys (AAR). Moreover in SUC there is a breaking of the doublet AUU, AUA merging with the doublet AUU in a triplet encoding for Ile. It is tempting to draw the conclusion that, when the push to form a larger multiplet acts only on some codons, the nature seems to choose to have a larger variety of a.a. choosing the codons subject to misreading or as stop or to encode affine a.a.. As a final remark, modelising the transversions simply by the vector operator $\tau_{H,O}^1 \otimes \tau_{V,-1}$ in eqs. \((3)-(4)\) we obtain the clear merging of eight doublets in four quartets (CCN, CGN, GCN, GGN), which are indeed the ”strongest” quartets involving a triple hydrogen bond.

### 3.2 Substitutions of 1st nucleotide

We study first the transitions using the crystal vector operators introduced in eq. \((2)\) with $b = 1$ acting on the first nucleotide. So we study the transition

$$\psi(CNX) \circ (\tau_{H,-1}^1 \otimes \tau_{V,0}^1) \implies \psi(UXN)$$

$$\psi(GNX) \circ (\tau_{H,-1}^1 \otimes \tau_{V,0}^1) \implies \psi(AXN)$$

\((16)\)

One computes that only the following transitions are allowed:

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\(^2\)For an explanation of this affinity, which is indeed observed, in the framework of the crystal basis model see [8]
1. in the quartets CUN and CCN, for the states with N = U, A

2. in the quartets CGN, GGN, GCN and GUN and in the doublets CAY and GAY for the states with N = U, Y = U

According to the strategy of protection of the "weakest" codon above outlined, a fusion of a doublet with a quartet in a sextet or with another doublet in a quartet (resp. of two quartets into an octet) happens if at least the transition of the codon with C or A in 3rd position (resp. of the codons with C and A in 3rd position) is allowed. In the light of the above criterion only the merging of the doublet UUR and the quartet CUN in a sextet is expected and, indeed, we obtain the sextet encoding Leu. Then let us analyse the transversions in first position

\[
\psi(CXZ) \circ (\tau_{H,0}^1 \otimes \tau_{V,-1}^1) \implies \psi(GXZ) \quad (17)
\]

\[
\psi(UXZ) \circ (\tau_{H,0}^2 \otimes \tau_{V,-1}^1) \implies \psi(AXZ) \quad (18)
\]

\[
\psi(CXZ) \circ (\tau_{H,-1}^c \otimes \tau_{V,-1}^1) \implies \psi(AXZ) \quad (19)
\]

where \( c = 1 \) if the codons CXZ and UXZ belong to the same irrep. and \( c = 2 \) otherwise. It turns out:

- eq.(17) allows only the transversions CCG → GCG, CCA → GCA, CGA → GGA, CAG → GAG and CGG → GGG
- eq.(18) allows only the transversions UCG → ACG and UGG → AGG
- eq.(19) allows only the transversions CCA → ACA, CGA → AGA, CUG → AUG and CAG → AAG.

As a consequence the doublet AGR merge into the quartet CGN forming another sextet encoding for Arg. Remark that the established pattern remains unchanged if the rank of \( \tau_H \) in both eqs.(17)-(18) is fixed 1 or 2. So at this stage the multiplet structure of the 64 codons is: 2 sextet, 6 quartets and 14 doublets, 2 of which are splitted in singlets. We get almost the structure of the VMC or of SUC, the Ser sextet being missed.

An alternative mathematical scheme to modelise the transition is:

\[
\psi(CXN) \circ (\tau_{H,-1}^1 \otimes \tau_{V,0}^0) \implies \psi(UXN) \quad (20)
\]

One computes that the following transitions happen:

1. in the quartets CCN, CGN, CUN, GGN, GCN and GUN for the states with N = U, A

2. in the doublets CAR, CAY, GAR and GAY for the states with R = A, Y = U

According to the strategy above outlined, we expect:

1. the fusion of the doublets CAR and UAR and GAR and AAR respectively in two quartets
2. the fusion of the doublets UUR (resp. UGR, AUR, AGR) and the quartets CUN (resp. CGN, GUN, GGN) in sextets.

A way to satisfy the stability condition without decreasing the number of a.a. synthetized is to make an appropriate choice for the stop codons, as already remarked. In fact the decreasing of an encoded a.a. is avoided choosing UAR as stop codons. Moreover the doublet UUR merges with the quartet CUN in the sextet encoding Leu, while in VMC UGR encodes a rare a.a. Trp and in SUC the doublet is splitted in two singlets, UGG encoding Trp and UGA, state subject to mutation, encoding Ter. The fusion of AGR with GGN does not happen, but in VMC this doublet encodes for stop codons and in SUC merges in another sextet, as we shall see below, while the quartet GAR and AAR is not found. However it is worth to note that some physical-chemical properties of the two encoded a.a. (Glu and Lys) are very close, see [5], and that the two codons are formed only by purine, with prevailing nucleotide A. May be also that the requirement of the merging of two doublets into a quartet when only the codon with a A nucleotide in the final position is subject to error, is a too strong condition. So we have found further arguments in favour of UAY and AGY being stop codons. Then let us analyse the tranversion \( C \rightarrow A \) which can be read as the result of \( C \rightarrow G \rightarrow A \) due to the tensor operator

\[
\tau^1_{H,-1} \oplus \tau^1_{V,-1}
\]  

(21)

It turns out that only the transversion \( CXA \rightarrowAXA \) is allowed. As a consequence we expect the merging of the doublet AGR with the quartet CGN, of the doublet AUR with the quartet CUN and, eventually, of the two doublets AAR and CAR. Only the first sextet is observed, but the doublet AUR encodes the starting codon in VMC and is split out in SUC.

### 3.3 Substitution of central nucleotide

The translation errors in the 2nd nucleotide occur very rarely, so we consider it as weak intensity effect, assuming that it cannot modify the already established pattern in doublets and quartets, but only to possibly cause the merging of whole multiplets. We modelise the transitions as

\[
\psi(XCN) \circ (\tau^1_{H,-1} \otimes \tau^2_{V,0}) \implies \psi(XUN)
\]

\[
\psi(XGN) \circ (\tau^1_{H,-1} \otimes \tau^2_{V,0}) \implies \psi(XAN)
\]

(22)

From the results of previous subsections we know that the codons with C or G in first position and C or U in the central position are organised in quartets, therefore only an octet is the possible larger multiplet. According to the general strategy followed, the fusion of two quartets is possible if at least the following transitions \( VCK \rightarrow VUK \) (\( V = C, G; K = C, A \)) are allowed. For the codons with U or A in first position and C in second position the fusion of a quartet WCK (\( W = U, A \)) and a doublet WUR (resp. WUY) in a sextet is possible if at least the transition \( WCA \rightarrow WUA \) (resp. \( WCC \rightarrow WUC \)) is possible. The fusion in sextet of a quartet VGN (\( V = C, G \)) with a doublet VAR (resp. VAY) is possible if at least the transition \( VGA \rightarrow VAA \) (resp. \( VGC \rightarrow VAC \)). Finally the fusion of two doublets WGR and WAR (\( W = U, A \)) (resp. WGY and WAY) should take place if at least the transition \( WGA \rightarrow WAA \) (resp. WGC
is allowed. It turns out that all the above listed transitions are forbidden. Indeed only the transitions CCC → CUC and GCC → GUC are allowed.

Let us analyse the tranversions in second position

\[
\psi(XCZ) \circ (\tau_{H,0}^1 \otimes \tau_{V,-1}^2) \implies \psi(XGZ)
\]

\[
\psi(XUZ) \circ (\tau_{H,0}^2 \otimes \tau_{V,-1}^2) \implies \psi(XAZ)
\]

\[
\psi(XCZ) \circ (\tau_{H,-1}^c \otimes \tau_{V,-1}^2) \implies \psi(XAZ)
\]

where \( c = 1 \) if the codons XCZ and XUZ belong to the same irrep. and \( c = 2 \) otherwise. It turns out:

- eq.(23) allows the transversions MCC → MGC (\( M \neq C \))
- eq.(24) does not allow any transversion
- eq.(25) allows only the tranversions CCC → CAC, UCU → UAU and ACU → AAU.

It turns out that one should expect the fusion in a sextet of the quartet UCN and of the doublet UGY as the transition UCC → UGC is allowed. This sextet does not appear in the genetic code, but as we shall see in the following subsection indeed the quartet UCN merges with the doublet AGR. One should also expect the fusion in a sextet of the quartet CCN and the doublet CAY, which indeed does not happen. Both these results suggest that the misreading of the central nucleotide is a very weak effect, if not enhanced by the simultaneous misreading of the first nucleotide, see the following Subsection. Remark that in eq.(23) we might write \( \tau_{H,0}^2 \) which leaves the final result unchanged (with this choice also the transition CCC → CGC is allowed).

### 3.4 Substitution of two nucleotides

The reading errors in a couple of nucleotides is an event occurring less frequently than the translation errors of one nucleotide in last or initial position, therefore we generally expect a weaker effect than the previously considered one nucleotide change. Consequently we assume that they cannot modify the already established pattern in doublets and quartets. So we consider only the possible action on the two initial nucleotides. The transition and tranversion of the first (second) nucleotide is modelised by the same operator used for the translation or tranversion on the first nucleotide, see eqs.\((19),(17),(18),(19)\) (see eqs.\((22),(23),(24),(25)\)). In the following we denote with a lower label the position of the nucleotide where the operator acts. The action of the two-nucleotides operators has to be computed in the following way: as first step one has to compute the action of the operator labeled by I giving rise to a "virtual" state with the labels assigned by the action of the relevant operator on the initial state of the codon, then one considers the action of the operator labeled by II on the "virtual" state and gets the labels of the final state. If these labels are the ones denoting in Table 1 the state corresponding to the codon, the transition is allowed. For example to analyse the transition CCN in UUN one should compute

\[
\psi(CCN) \circ (\tau_{H,-1}^1 \otimes \tau_{V,0}^1)_I \rightarrow \psi((UCN)_v)
\]

\[
\psi((UCN)_v) \circ (\tau_{H,-1}^1 \otimes \tau_{V,0}^1)_I \rightarrow \psi(UCN)
\]

(26)
where the labels of the state \((UCN)_v\) are computed by

\[
\psi((UCN)_v) = \psi(CCN) \otimes (\tau^1_{H,-1} \otimes \tau^1_{V,0})_I
\]  

(27)

It follows that one can get an allowed transition and/or transversion to a final state, even if the action of the operator labelled by I does not induce it. The same kind of computation has to be performed in the cases of transition + tranversion or vice versa or double tranversion. Let us analyse:

- **the double transitions**

\((CCN \to UUN, GGN \to AAN, CGN \to UAN, GCN \to AUN)\)

\[
(\tau^1_{H,-1} \otimes \tau^1_{V,0})_I \oplus (\tau^1_{H,-1} \otimes \tau^2_{V,0})_{II}
\]  

(28)

Only the transitions CCU \(\to\) UUU and GCU \(\to\) AUU are allowed. Note that obtained pattern is unmodified if we modelise the double transition by

\[
(\tau^1_{H,-1} \otimes \tau^0_{V,0})_I \oplus (\tau^2_{H,-1} \otimes \tau^0_{V,0})_{II}
\]  

(29)

- **the transition + tranversion:**

\((CCN \to UGN, CUN \to UAN, GCN \to AGN, GUN \to AAN)\)

\[
(\tau^1_{H,-1} \otimes \tau^1_{V,0})_I \oplus (\tau^b_{H,0} \otimes \tau^2_{V,-1})_{II}
\]  

(30)

where here and in the following \(b = 1\) \((b = 2)\) for transversion \(C \to G\) \((U \to A)\). Only the transition CUC \(\to\) UAC is allowed.

\((CCN \to UAN, GCN \to AAN)\)

\[
(\tau^1_{H,-1} \otimes \tau^1_{V,0})_I \oplus (\tau^2_{H,-1} \otimes \tau^2_{V,-1})_{II}
\]  

(31)

Only the transitions CCU \(\to\) UAC and GCU \(\to\) AAU are allowed.

- **transversion + transition:**

\((CCN \to GUN, CGN \to GAN, UCN \to AUN, UGN \to AAN)\)

\[
(\tau^b_{H,0} \otimes \tau^1_{V,-1})_I \oplus (\tau^1_{H,-1} \otimes \tau^2_{V,0})_{II}
\]  

(32)

Only the transversion-transitions CUC \(\to\) GUY are allowed.

\((CCN \to AUN, CGN \to AAN)\)

\[
(\tau^1_{H,-1} \otimes \tau^1_{V,-1})_I \oplus (\tau^1_{H,-1} \otimes \tau^2_{V,0})_{II}
\]  

(33)

Only the transversion-transition CCU \(\to\) AUU is allowed.
• double transversion:

\[(CCN \rightarrow GGN, CUN \rightarrow GAN, UUN \rightarrow AAN, UCN \rightarrow AGN)\]

\[(\tau_{H,0}^b \oplus \tau_{V,-1}^1)_I \oplus (\tau_{H,0}^b \oplus \tau_{V,-1}^2)_{II}\] (34)

Only the transversions \(UCC \rightarrow AGC\) and \(CCC \rightarrow GGC\) are allowed.

\[(CCN \rightarrow AGN, CUN \rightarrow AAN)\]

\[(\tau_{H,-1}^1 \oplus \tau_{V,-1}^1)_I \oplus (\tau_{H,0}^2 \oplus \tau_{V,-1}^2)_{II}\] (35)

No transversion is induced.

\[(CCN \rightarrow GAN, UCN \rightarrow AAN)\]

\[(\tau_{H,O}^b \oplus \tau_{V,-1}^1)_I \oplus (\tau_{H,0}^b \oplus \tau_{V,-1}^2)_{II}\] (36)

Only the transversion \(CCG \rightarrow GAG\) is allowed.

\[(CCN \rightarrow AAN)\]

\[(\tau_{H,-1}^1 \oplus \tau_{V,-1}^1)_I \oplus (\tau_{H,-1}^2 \oplus \tau_{V,-1}^2)_{II}\] (37)

Only the transversion \(CCG \rightarrow AAG\) is allowed.

It turns out, using also the results and the discussions of the previous subsections, that the action of the above operators does not modify the established pattern except the one given by eq.(34) which induces the mutation \(UCA \rightarrow AGA\), so urging the doublet AGR to merge with the quartet UCN giving rise to the third sextet encoding for Ser.

4 Conclusions

Before discussing what we have obtained, let us summarize what we have done. The starting point is the observed pattern in multiplets of the genetic code. From its invariance in time and from its, almost, universal character we infer that such a pattern has to ensure an efficient and stable translation in the building of polypeptides chains, i.e. it is error proof against the most frequent reading errors. To give a quantitative and precise meaning to this statement we need to build a mathematical model both for the genetic code and for the misreading mechanisms. In the crystal basis model each codon is represented as a state \(\psi_{(J_H, J_V, J_{H,3}, J_{V,3})}\) in the module space of \(U_{q-0}(sl(2) \oplus sl(2))\). The 64 states are separated in nine different invariant subspaces labelled by a couple of half-integer \(J_H, J_V\). The mechanisms implying translation errors are modelised by suitable tensor operator, with definite transformation properties under \(U_{q-0}(sl(2) \oplus sl(2))\), which may or may not relate two states of such states. If the states are connected, we infer that they can be mistaken in the translation process, and therefore, in order to ensure in case of misreading the synthesis of the same a.a., the corresponding codons have to be synonymus. By studying the action of the operators, we obtain the splitting of the 64 states in a set of multiplets representing almost faithfully the degeneracy of the genetic code. The simple proposed mathematical modelisation is able, in an amazing way, to account
almost for the existence of only 20 a.a. and, almost, for the structure of the VMC and SUC. Why the nature uses the 20 particular a.a., enumerated in the beginning of this paper, in the practically unlimited variety of these molecules is still to be understood and, of course, is far beyond the aim of this work. The structure of the mathematical operators used to model transitions and transversions is simple but arbitrary. Therefore it is worth to discuss in a more quantitative way the extent of the obtained results. Let us use as starting point the pattern of the 64 codons grouped in 32 doublets, even if this result is less obvious that one can naively think of. Indeed from Table 1 one realizes that 8 of the 16 doublets of the form XZY (resp. XZR) belong to different irreps. Therefore the vector operator given in eqs. (8), (9) operates in half the case as a generator and in half case as an intertwining operator. The transversion operator induces the merging of 16 doublets in 8 quartets in full agreement with the observed pattern of the genetic code. The formation of only 8 quartets, with the correct content in the first two nucleotides, induced by the action of operator eqs. (10), (11), (12) is a good result, especially considering that the number of different choices of 8 quartets in 16 doublets is 12870. Once formed the quartets the operator eq. (16) induces the formation of 2 sextets which are the correct ones between the 420 possibilities. Finally the operator eq.(34) induces the formation of the correct 3rd sextet between 24 possibilities. In conclusion it is extremely surprising that such an arbitrary choice explains why and in which pattern of multiplets (with a probability to find the correct pattern of about $7,7 \cdot 10^{-9}$) the remaining 60 codons encode only 20 amino acids. We have investigated the dependence of the pattern obtained from the structure of the tensor operators used to modelise the misreading process. Differences do appear in the different modelisations studied, but most of the pattern of the genetic code is obtained, showing that there is a bulk of its organisation little sensitive to the details of the operators modelling the misreading process. This feature appears also in other modelisation not discussed in the paper, e.g. modelling the transition and transversion as a two steps process: deletion of a nucleotide and subsequently creation of a different one. A very few differences, depending also from the choosen scheme, exist between the theoretical pattern of organisation in multiplets and the observed one. In particular some minor changes in the eukaryotic code do not find an explanation in the model, even if for some of them the model give hints in the correct direction. Furthere refinements or, more probably, the presence of some other mechanism whose action is not modelisable by crystal tensor operators may account for these changes and for the not appearance of an expected 4th sextet in the second mathematical scheme. However it should remarked that this sextet is formed by CCN and CAY where CC (resp. CA) is the highest weight (resp. the lowest weight) in the dinucleotide set.

In our model the strategy followed by the genetic code seems to be adressed to keep the most variety of encoded amino acids consistently with a reasonable level of protection of the codons against the most common translation errors. A fundamental problem, not all faced in this paper, is the reason for the observed correspondence between multiplets and amino acids; in other words once obtained the organisation in different multiplets of the genetic code, there is a mechanism imposing which particular amino acids have to be encoded by sextets, quartets and so on or it is just a random event ? Stereochemical hypothesis [3], [4] suggests that the physical-chemical properties of the amino acids play a crucial role to determine the
correspondence between multiplets and amino acids. A clear shortcoming of the model is the fact that the analysis of the formation of the different multiplets is performed in a "static" manner while it is believed, although no unambiguous model does exist, that an evolution of the genetic code and of the corresponding encoded amino acids has happened. It is indeed in the evolution that rules and properties of the systems which are necessary to the existence of living organisms are fixed and selected. The selection, which dominates biology, has not at all taken into account in the present oversimplified model. However hopefully this kind of reasoning can be applied to models describing the evolution process. One may argue that, in a more refined model, different operators should be used to modelise different mutagenic effects, whose role and intensity depend on the in time changing environment. We point out also that the one may conjecture to modelise spontaneous and induced mutations of the genetic code by suitable tensor operators, a first analysis of this type has been given in [8]. In conclusion the model presented in this paper states that the genetic code is what it is because it is ”optimized”, at least for the environment in which it was formed, and not for a freezing random event. Of course the word optimization should be taken in a loose sense as we have not quantitatively described the gain of the different choice. We believe that in this context methods of game theory can be appropriately used to a better description.

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References

[1] B.K. Davies, Evolution of the genetic code, Prog.Biophys.Mol.Biol. 72 (1999) 157

[2] L. Frappat, A. Sciarrino, P. Sorba, A crystal base for the genetic code, Phys. Lett. A 250 (1998) 214, physics/9801027.

[3] M. Kashiwara, Crystallizing the q-analogue of universal enveloping algebras, Commun. Math. Phys. 133 (1990) 249.

[4] V. Marotta, A. Sciarrino, Tensor operator and Wigner-Eckart theorem for $U_{q=0}(sl(2))$, J. Math. Phys. 41 (2000) 5735, math.QA/9811143

[5] L. Frappat, A. Sciarrino, P. Sorba, Predictions of Physical-Chemical Properties of Amino Acids from Genetic Code, physics/0007034.

[6] C.R. Woese, The genetic code, Harper and Row, New York (1967).

[7] M. Shimizu, Molecular basis for the Genetic Code Origin, J.Mol.Evol. 18 (1982) 297.

[8] L. Frappat, A. Sciarrino, P. Sorba, Crystalizing the Genetic Code, physics/0003037.
Table 1: The vertebral mitochondrial code. The upper label denotes different irreducible representations. In bold character the amino acids which are encoded differently in the eukariotic or standard code: UGA, AUA, AGY encoding respectively for Ter, Ile and Arg.

| codon | a.a.  | \(J_H\) | \(J_V\) | \(J_{3.H}\) | \(J_{3.V}\) | codon | a.a.  | \(J_H\) | \(J_V\) | \(J_{3.H}\) | \(J_{3.V}\) |
|-------|-------|--------|--------|----------|----------|-------|-------|--------|--------|----------|----------|
| CCC   | Pro   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | UCC   | Ser   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| CUC   | Leu   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | UUC   | Phe   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| CGC   | Arg   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | CGC   | Cys   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| CAC   | His   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | CAC   | Tyr   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| GCC   | Ala   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | GCC   | Thr   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| GAC   | Asp   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | GAC   | Ser   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| GAU   | Asp   |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | GAU   | Asn   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| GAG   | Glu   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | GAG   | Lys   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| GAA   | Glu   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) | GAA   | Lys   |  \(\frac{3}{2}\) |  \(\frac{3}{2}\) |  \(\frac{1}{2}\) |  \(\frac{1}{2}\) |
| dinucl. | $J_H$ | $J_V$ | $J_{3,H}$ | $J_{3,V}$ | dinucl. | $J_H$ | $J_V$ | $J_{3,H}$ | $J_{3,V}$ |
|--------|-------|-------|----------|----------|--------|-------|-------|----------|----------|
| CC     | 1     | 1     | 1        | 1        | UC     | 1     | 1     | 0        | 1        |
| CG     | 1     | 0     | 1        | 0        | UG     | 1     | 0     | 0        | 0        |
| CU     | 0     | 1     | 0        | 1        | UU     | 1     | 1     | -1       | 1        |
| CA     | 0     | 0     | 0        | 0        | UA     | 1     | 0     | -1       | 0        |
| GC     | 1     | 1     | 1        | 0        | AC     | 1     | 1     | 0        | 0        |
| GG     | 1     | 1     | 1        | -1       | AG     | 1     | 1     | 0        | -1       |
| GU     | 0     | 1     | 0        | 0        | AU     | 1     | 1     | -1       | 0        |
| GA     | 0     | 1     | 0        | -1       | AA     | 1     | 1     | -1       | -1       |