# Symmetry scheme for amino acid codons

J. Balakrishnan \*

CSIR Centre for Mathematical Modelling and Computer Simulation (C-MMACS), NAL Wind Tunnel Road, Bangalore–560 037, India (Received 30 July 2001; published 25 January 2002)

Group theoretical concepts are invoked in a specific model to explain how only twenty amino acids occur in nature out of a possible sixty four. The methods we use enable us to justify the occurrence of the recently discovered 21st amino acid selenocysteine, and also enables us to predict the possible existence of two more, as yet undiscovered amino acids.

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# I. INTRODUCTION

The genetic code uses four "letters" or the bases adenine (A), thymine (T), guanine (G) and cytosine (C) in the four nucleotides constituting the DNA [or uracil (U) in the corresponding RNA template] by reading them in groups of three. A and G are purine bases while C and T are pyrimidines. Like T, U pairs with A. During protein synthesis, these triplets of three bases (or codons) encode for specific amino acids. The genetic code however, is degenerate, and even though there are 64 possible codons, only 20 amino acids relevant to mammalian proteins actually occur in nature. It has remained intriguing that despite the redundancy of the codons, the genetic code did not expand any further and stopped at the number 20. It is therefore of interest to find out if the genetic code has any mathematical property which gets optimized when the number of codons becomes nearly thrice the number of the amino acids. We attempt here to answer this question by adapting some standard group theoretical methods of particle physics to molecular biology. The genetic code is nearly the same for all organismsnoncanonical genetic codes are used in mitochondria and some protozoa [1]. Here, we consider only the universal genetic code.

Out of the 64 possible codons, it is now known that 61 codes for the known 20 amino acids—the remaining three (UAG, UGA, and UAA) code for termination or "stop" codons. The codon AUG for methionine also codes for the initiation of the translation process, and is therefore also called the "start" codon. It was discovered some years back that one of the stop codons, UGA, translates under certain circumstances to a 21st amino acid selenocysteine [2]. It is certainly conceivable, that the other two stop codons UAG and UAA similarly code also for some as yet undiscovered amino acids.

Our approach is a semiempirical one, but it enables us to not only justify the occurrence of selenocysteine, but it allows us also to predict the possible existence of two more, as yet undiscovered amino acids. We look at the hydrophilic and hydrophobic tendencies of the amino acid residues constituting the proteins, as they play a key role in determining the conformation of a protein and the way it folds.

The idea of using group theoretical techniques in studying

the genetic code is not new—Refs. [3] deals in length with searches for symmetries among Lie groups for trying to explain codon degeneracy in the genetic code. In their very interesting papers, the authors of [3] view the universal genetic code as having evolved through a chain of successively broken-symmetry events, from a primordial amino acid having a particular symmetry [which they assume to be Sp(6)]. Their approach, however, does not presently account for the 21st amino acid selenocysteine having properties similar to cysteine.

We approach the problem from a different point of view: we have tried to show that it is possible to classify the 64 possible codons into well-defined multiplets—the hydropathic properties of the amino acids they code for are determined by the multiplet they belong to. Our approach has also a predictive power (presently lacking in the papers in [3]), enabling one to approximately predict certain properties of two other possible, as yet undiscovered amino acids.

### **II. THE ROLE OF CODONS IN PROTEIN SYNTHESIS**

Protein synthesis is initiated by a process called transcription in which the cell makes a copy of the gene-a messenger RNA (or mRNA) template, from the DNA with the help of an enzyme called RNA polymerase [1,4]. Transcription stops when the enzyme reaches a "stop" sequence at the end of the gene, upon which the mRNA dissociates from the DNA, moves to the cytoplasm, and gets attached at its Shine-Dalgarno sequence to a ribosomal RNA (rRNA) located within the ribosome. In the cytoplasm, transfer RNA (tRNA) molecules form complexes called aminoacyl-tRNAs with their respective amino acids, in a process driven by the enzymes aminoacyl-tRNA synthetases. An aminoacylated tRNA moves to the ribosome where its anticodon recognizes its corresponding complementary codon of the mRNA and incorporates the amino acid residue at the correct position specified by the mRNA codons into a growing peptide chain of the protein, this process being called translation. The folds governing the conformation of a protein are thus determined by its primary structure—the sequence of the amino acids in the peptide chain, which in turn depend upon the sequence of codons in the functionally mature mRNA and the exon sequences in the DNA.

#### **III. GROUP THEORETICAL METHODS FOR CODONS**

Keeping all of the above complex dynamics in mind, one could still try to look for any possible symmetries in the

<sup>\*</sup>Email address: janaki@cmmacs.ernet.in

system, and see whether a much-simplified, minimal mathematical model for the codons could capture any of the physics and biochemistry of the actual biological system.

To begin with, we first recall the basic chemical structure of an amino acid. It has a central carbon called the  $\alpha$  carbon which is attached to four groups—a hydrogen atom, an acidic carboxyl (–COOH) group, a basic amino (–NH<sub>2</sub>) group, and a distinct side chain (–R) group—this last group essentially determines its chemical properties.

The amino acids we know, can be classified into two broad categories on the basis of their solubilities in water: hydrophobic and hydrophilic. At pH 7.0, hydrophobic (nonpolar) –R groups are contained by alanine, valine, leucine, isoleucine, proline, phenylalanine, tryptophan, methionine, cysteine, and glycine. Hydrophilic side chains are polar, so that they can be further classified as acidic, basic, or neutral, depending upon their charges—at pH 7.0, lysine, arginine, and histidine have basic side chains, aspartate and glutamate are acidic and there are those which have polar but neutral side chains: asparagine, glutamine, serine, threonine, and tyrosine. Yet another consideration for classification of amino acids could be on the basis of whether the side chains are aliphatic or aromatic.

The categories or multiplets into which the amino acids fall, appear to reflect certain underlying internal symmetries. We know that while the base triplets (codons) do not constitute the amino acids, the base sequence within each codon dictates the identification of and translation to a particular amino acid. We can therefore hypothesize that the bases possess certain basic symmetries.

We look for the properties of the system which do not change or only approximately change in time, and the symmetries associated with the conserved quantities.

Let T(a) represent a group of transformations which leave the Hamiltonian H of the physical system invariant. We assume that the transformations are represented by unitary operators U(a), ("a" denoting a parameter of the transformation) operating on a complex vector space [5]. The eigenvalue equation for the system would be

$$H\phi_n = E_n \phi_n, \tag{1}$$

where  $\phi_n$  is an eigenfunction of *H* with energy eigenvalue  $E_n$ . Operating on this with U(a), one obtains

$$UH\phi_n = UHU^{-1}U\phi_n = E_nU\phi_n,$$
  
or  $H'\phi'_n = E_n\phi'_n,$  (2)

where we have let

$$H' = UHU^{-1}$$
 and  $\phi'_n = U\phi_n$ . (3)

Since U leaves the Hamiltonian invariant: H' = H, the state  $\phi'_n$  has the same energy as the state  $\phi_n$ . Operating on  $\phi_n$  with U(b), "b" being another parameter, would give another eigenstate of H with the same energy  $E_n$ . The states which one obtains by operating with all U on a given state can be expressed as linear combinations of a set of basis vectors spanning the subspace of eigenstates of H with a given en-

ergy. In general these vectors are the basis vectors of an irreducible representation and denote a set of states called a multiplet. All states of a multiplet are degenerate in the energy.

These basic techniques can be used to develop a symmetry scheme for the nucleotides and the codons. A and G can be regarded as different states of the same object, the purine, described by a state vector in an abstract, complex vector space, and similarly, C and T/U as different states of a pyrimidine. The purine and the pyrimidine state vectors are then each, two-component matrices :

$$\psi_R = \begin{pmatrix} A \\ G \end{pmatrix}$$
 and  $\psi_Y = \begin{pmatrix} C \\ T \end{pmatrix}$  or  $\begin{pmatrix} C \\ U \end{pmatrix}$ ,

where  $\psi_R$  and  $\psi_Y$  denote the purine and pyrimidine state vectors, respectively. A unitary transformation  $U(\Lambda)$  which involves a rearrangement of the components, but which leaves the magnitude  $(\bar{\psi}_i\psi_i)^{1/2}$ , (i=R,Y) invariant can be written as

$$\psi'_{i} = U(\Lambda)\psi_{i}. \tag{4}$$

Transition mutations involving the replacement of one purine by another purine, or one pyrimidine by another pyrimidine can be represented by Eq. (4). The states representing A and G could be taken to correspond, respectively, to "up" and "down" states of  $\psi_R$ , with respect to a chosen axis in the internal vector space. A state intermediary between these two states could be regarded as a superposition of the two states, with the state having the larger probability measure, having the higher possibility of becoming the final state of the mutation. Proceeding similarly, we can define the full system of all the four bases by a four-component vector  $\phi^i$  (i = 1, ..., 4).

$$\vec{\phi} = \begin{pmatrix} A \\ G \\ C \\ U \end{pmatrix}.$$

A rotation through an angle  $\vec{\Lambda}$  in this internal space which transforms  $\vec{\phi}$  to  $\vec{\phi}'$ .

$$\vec{\phi} \to \vec{\phi}' = e^{i\vec{\mathbf{l}}\cdot\vec{\Lambda}}\vec{\phi},\tag{5}$$

where  $I^k$  are "k" number of  $4 \times 4$  matrices, and are representations of the generators of the transformation group, changes the state of the nucleotide system, but not the total number of nucleotides. Transversion mutations in which a purine is replaced by a pyrimidine, or vice versa, are also covered by the transformation (5).

Since there are four different kinds of bases out of which three together code for one amino acid, we view the amino acids as arising out of "three-base" representations of the group SU(4). The purine and pyramidine bases are both hydrophobic and are turned inwards in the DNA structure. The four bases are distinguished by three conserved numbers

		Secon	d Position			
	U	С	Α	G		
	-1/2 (F)	-1/2(S)	0(Y)	-1/2(C)	U	
U	1/2 (F)	1/2~(S)	0 (Y)	1/2 ( <i>C</i> )	С	
	-1/2 ( <i>L</i> )	1/2(S)	0 (stop)	0 (SeC)	Α	
	1/2~(L)	-1/2(S)	0 (stop)	0 (W)	G	
Р	-1 ( <i>L</i> )	-1/2(P)	-1/2 ( <i>H</i> )	-1(R)	U	P
2	0 ( <i>L</i> )	0(P)	1/2 ( <i>H</i> )	0 (R)	С	0
s C	0 ( <i>L</i> )	0 ( <i>P</i> )	-1/2(Q)	0(R)	Α	S
i	1(L)	1/2 ( <i>P</i> )	1/2(Q)	1 ( <i>R</i> )	G	i
t						t
i	-1/2 ( <i>I</i> )	-1 ( <i>T</i> )	-1/2 (N)	-1 (S)	U	i
)	0 (I)	0 ( <i>T</i> )	1/2 ( <i>N</i> )	1(S)	С	0
ı A	1/2 (I)	0 ( <i>T</i> )	-1/2 (K)	-1/2 (R)	Α	п
	0 ( <i>M</i> )	1(T)	1/2 ( <i>K</i> )	1/2 (R)	G	
1						3
	-3/2(V)	-1/2(A)	-1 (D)	-1 (G)	U	
	-1/2 (V)	1/2 (A)	1 (D)	0 ( <i>G</i> )	С	
G	1/2 (V)	1/2(A)	0 ( <i>E</i> )	1 (G)	Α	
	3/2 (V)	-1/2(A)	0 ( <i>E</i> )	0 ( <i>G</i> )	G	

TABLE I.  $J_1$ .

which we denote by  $J_1$ ,  $J_2$ , and  $J_3$  [which reflects the rank three of the SU(4) group]. This collection of four states serves as the basis vectors for a fundamental representation of SU(4). A model with four bases could certainly correspond to a completely different symmetry group and not necessarily SU(4)—we consider however, this possibility only.

The base triplets formed from the Kronecker product of three fundamental representations of SU(4), and arranged in the different multiplets (which are the decompositions of the product) represent at those positions, the amino acids they code for.

$$4 \otimes 4 \otimes 4 = 20_{\mathrm{S}} \oplus 20_{\mathrm{M}} \oplus 20_{\mathrm{M}} \oplus \overline{4}, \qquad (6)$$

where **4** is the fundamental representation of SU(4),  $\overline{4}$  is the conjugate representation, and the subscripts **S** and **M** denote states which are formed from the symmetric combinations and the mixed-symmetry combinations, respectively, of the product tensors.

Each multiplet is the realization of an irreducible representation of SU(4), and because the members of each have masses which are not exactly, but only nearly degenerate, the SU(4) symmetry is only an approximate symmetry. Notice that the total codon count of 64 is respected, but now the codons are grouped in separate multiplets. Each multiplet has a characteristic property which is shared by all its members.

Since the bases do not themselves constitute the amino acids, it follows that though the  $J_i$  ( $i=1,\ldots,3$ ), are conserved numbers for the codons, they need not necessarily be additively conserved for the Kronecker product, since the permutations of the bases within a triplet only *code* to different amino acids.

TABLE II.  $J_2$ .

		Seco	nd Position			
	U	С	Α	G		
	-1 (F)	-1 (S)	0 (Y)	1 ( <i>C</i> )	U	
	-1 (F)	1(S)	0 (Y)	1 ( <i>C</i> )	С	
U	0(L)	-1(S)	-1 (stop)	0 (SeC)	Α	
	0 ( <i>L</i> )	1 (S)	0 (stop)	-1 (W)	G	
Р	1 ( <i>L</i> )	0 ( <i>P</i> )	1 (H)	1 (R)	U	Р
0	-1 ( <i>L</i> )	0 ( <i>P</i> )	1 (H)	1 ( <i>R</i> )	С	0
s C	1 (L)	1 (P)	1(Q)	1 ( <i>R</i> )	Α	S
i	1 (L)	0(P)	1(Q)	1 ( <i>R</i> )	G	i
t						t
i	1 (I)	1 ( <i>T</i> )	-1 (N)	0 (S)	U	i
o A	0 (I)	1 (T)	-1 (N)	0(S)	С	0
п	1 (I)	1 (T)	0 ( <i>K</i> )	0(R)	Α	п
	1 (M)	1 (T)	0 ( <i>K</i> )	0(R)	G	
1						3
	1 (V)	0 (A)	0 (D)	0(G)	U	
	1 (V)	0(A)	0 (D)	0(G)	С	
n G	1 (V)	0(A)	0 ( <i>E</i> )	0(G)	Α	
	1 (V)	0 (A)	0 ( <i>E</i> )	-2(G)	G	

We find that when we group together the amino acids into four categories: hydrophobic, weakly hydrophobic, hydrophilic, and imino, and then try to adapt the SU(4) quantum numbers [6,7] for the quark triplets (baryons) to the codons, they fall beautifully into well-defined categories, as follows.

The numbers  $J_i$  we have assigned for the base triplets are shown in Tables I–III, within the standard format of the universal genetic code. The alphabets within brackets in these tables are the conventional one-letter abbreviations for the various amino acids. The left-hand column stands for the base present at the first (5') position of the codon, the top row denotes that in the second (middle) position of the codon, and the right-hand side column indicates the one present in the third (3') position of the codon.

The three-dimensional plots of  $J_1$ ,  $J_2$ , and  $J_3$  for all the codons are shown in Figs. 1–4. Except for the case of proline (*P*), all the codons coding for a particular amino acid share the same  $J_3$  number.

All the amino acids in Fig. 1 are hydrophobic, and all in Fig. 3 are polar and hydrophilic. It is of course well-known that there exist several different hydrophobicity scales, and there is no unique assignment of clear-cut hydrophobicity values for amino acids [8]. The amino acids in Fig. 1, are, in general, widely accepted to be more hydrophobic than the others. We have classified proline (*P*) separately, as a realization of the conjugate  $\overline{4}$  representation of SU(4), although it is very hydrophobic, since it is technically an imino (–NH) acid rather than an amino (–NH<sub>2</sub>) acid, as its side chain is bonded to the nitrogen as well as to the central  $\alpha$  carbon.

The amino acids cysteine (C), threonine (T), alanine (A), tryptophan (W), serine (S), and tyrosine (Y) in Fig. 2 have been classified as weakly hydrophobic—in fact some of

		Seco	ond Position			
	U	С	Α	G		
	0(F)	0(S)	0(Y)	2 ( <i>C</i> )	U	
	0(F)	0(S)	0(Y)	2 ( <i>C</i> )	С	
U	1 (L)	0(S)	1 (stop)	2 (SeC)	Α	
	1 ( <i>L</i> )	0(S)	2 (stop)	1 (W)	G	
Р	1(L)	1 (P)	2 (H)	1 ( <i>R</i> )	U	Р
0	1 (L)	0(P)	2 ( <i>H</i> )	1 ( <i>R</i> )	С	0
s C	1 (L)	1 (P)	0 (Q)	1 ( <i>R</i> )	Α	S
i	1 (L)	1 (P)	0(Q)	1 ( <i>R</i> )	G	i
t						t
i	2 (I)	1(T)	0 ( <i>N</i> )	0 (S)	U	i
0	2 (I)	1 (T)	0 (N)	0(S)	С	0
n A	2 (I)	1 (T)	1 ( <i>K</i> )	1 ( <i>R</i> )	Α	п
	3(M)	1 (T)	1 (K)	1 ( <i>R</i> )	G	
1						3
	0 (V)	1(A)	0 ( <i>D</i> )	0 ( <i>G</i> )	U	
	0(V)	1(A)	0 (D)	0(G)	С	
G	0(V)	1(A)	0(E)	0(G)	Α	
	0 ( <i>V</i> )	1 (A)	0 ( <i>E</i> )	0 ( <i>G</i> )	G	

them are slightly hydrophilic—in some hydrophobicity scales, *S* and *Y* are categorized as being hydrophilic.

Notice that among the hydrophilic amino acids [hystidine (H), arginine (R), lysine (K), asparagine (N), glutamine (Q), aspartic acid (D), and glutamic acid (E)], H, R, and K are basic and occur with higher  $J_3$  values than the acidic amino acids (D, E).

It is interesting to note that in our model, of the nine essential amino acids which are required for protein synthesis by adult humans, two (H and K) represent the hydrophilic multiplet, two (T and W) represent the weakly hydrophobic multiplet, while all the amino acids except glycine (G) [methionine (M), isoleucine (I), leucine (L), valine (V), and phenylalanine (F)] in the hydrophobic multiplet are essential.

In general, the amino acids which have closer similarities between themselves, occur nearer to each other within each





FIG. 2. Weakly hydrophobic amino acids  $[20_M \text{ of } SU(4)]$ .

multiplet. The amino acids in each multiplet are also in close conformity with the standard suggested amino acid substitutions based on the Dayhoff matrix [9] wherein amino acid residues which are near to each other in the Dayhoff plot are good candidates for mutual exchange for conservative mutations in proteins.

It is extremely interesting that with the assignment of the  $J_i$  numbers as in Tables I–III, the codon UGA which usually codes for "stop," falls in the multiplet of weakly hydrophobic amino acids, and has the same  $J_3$  value of two as cysteine (C). UGA codes also for the recently discovered 21st amino acid selenocysteine (SeC)—the sulfur atom in C is replaced by selenium in SeC.

On the basis of these observations, one could similarly predict the existence of two more as yet undiscovered amino acids—the codons UAG and UAA which are presently known to code only for the "stop" signal. One could hypothesize that if UAG were to code for a (22nd) amino acid, then that would have properties similar to H, and similarly, UAA if coded for a 23rd amino acid would have properties similar to K or R, even though these two codons both differ from Y only at the wobble position.

In our symmetry scheme for codons, we have not yet found it possible to assign  $J_i$  numbers for each base individually so as to give additively, the total  $J_i$  numbers for each base triplet coding for the amino acids, in a consistent way. This is not unreasonable, since as emphasized before, the bases *do not* constitute the amino acids.



FIG. 1. Hydrophobic amino acids  $[20_s \text{ of } SU(4)]$ .



FIG. 3. Hydrophilic amino acids  $[20_M \text{ of } SU(4)]$ .



FIG. 4. Imino (proline)  $[\overline{4} \text{ of } SU(4)]$ .

Synonymous codons occur at different frequencies even though they all code for the same amino acid. Correspondingly, the tRNA molecule for the codon used more, occurs in larger amounts than its isoacceptors. This fact is reflected in the differing  $J_1$  and  $J_2$  values for synonymous codons. The probability for the occurrence of a particular synonymous codon would be weighted by  $J_i$ -dependent factors in the corresponding partition function and its free energy.

Thus, the occurrence of only 21 amino acids out of a possible 64, can be explained in a satisfactory manner within our scheme.

## **IV. DISCUSSION**

We have classified the 64 codons within a semiempirical model which very closely resembles the decomposition of the Kronecker product  $4 \otimes 4 \otimes 4$  of SU(4), after assuming that bases *A*, *C*, *G*, and *T/U* can be regarded as different states of a vector in an abstract, complex vector space. We represent transition and transversion mutations involving replacement of purines and pyramidines, by rotations through an angle in this internal space. Our model explains the existence of synonymous codons (thus explaining how 21 amino acids (including selenocysteine) have been found to occur so far out of a possible 64). It also enables us to predict the possible existence of two more, as yet undiscovered amino acids.

The stability of a fully folded native protein structure is a consequence of a balance between the hydropathies of the constituent amino acid residues in its primary structure, electrostatic interactions, and hydrogen bonding. It would thus be a useful exercise to incorporate the ideas in this paper in an analytical manner to approach the protein folding problem, since incorporation of all the internal symmetries into the partition function is essential to get the correct form of the free energy of the system.

Our ideas and methods could also be very useful in providing a rigorous mathematical basis for studying DNA replication and protein synthesis using quantum algorithms.

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