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# GENETIC CODE AS A UNIQUE SYSTEM

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AS A UNIQUE SYSTEM

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## PREFACE

This book is an attempt to focus attention on new understanding of the genetic code. The central theme is the Boolean spaces and genetic coding based on them. The mysteries of the genetic code are ultimately explained in terms of LIGHT (Logical, Information, Geometric, Homeomorphic, Topological) model and System.

After reading this book we can see that, there have been several reasons for its writing. First, until this book there is not good enough mathematical model to make link with physical reality of genetic code. Second, we can see that there is strong determination between atom and nucleon number of amino acids and their physical and chemical parameters. A third motive for this book is to make available a unified resource for teaching Ph.D. students. The book can also serve both researchers and students in the field of biochemistry, molecular biology and interdisciplinary studies.

Dr. Rakočević does a particularly excellent job of creating a working model of nucleon number (mass) and shell properties (electrons). The book thoroughly, clearly, and gently opens the reader's mind to the conclusion that we, as biological beings, are more than classical chemistry and physics entities.

In the past seven years, I have had the pleasure to be associated closely with Dr. Rakočević. I liked the book, have enjoyed reading it and think that is a timely contribution. As usually in science, we may do not agree with all of it but, in the main, Dr. Rakočević model of genetic code is more consistent with physical reality than any other model which I know.

There is no question that this book will have great influence on our thought about genetic code.

Prof. Dr. Djuro Koruga

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# 1. INTRODUCTION

In spite of the fact that the genetic code had been practically decoded as early as 1966 (Crick, 1966a), there are still many unanswered questions and controversies even today in relation to it. Among the unanswered questions, that is, the unsolved problems we list the following:

1. Is the genetic code really universal or not (Crick, 1968; Porschke, 1985; Alvager et al., 1989)?
2. If it makes sense, instead of a universal, to talk about the standard code, does an established connection, one defined by law or principle, with nonstandard codes (cf. Attardi, 1985; Alvager et al., 1989) then exist?
3. Being redundant, did the genetic code (in the process of evolution) really degenerate, or was it generated as such? (Caspari, 1968, p 327: "This code was completely degenerate and... each code letter was used in more than one codon.")?
4. As to the interpretations of the origin of the genetic code, to which of the two theories should preference be given: "The Stereochemical Theory" or "The Frozen Accident Theory" (Crick, 1968; Porschke, 1985); moreover, to what degree is the first theory supported by the Watson-Crick rules of base pairing (Watson & Crick, 1953a, 1953b), and to what degree is it thwarted by mispairing in the process of complementary base pairing as a condition for the origin of substitution mutations (Topal & Fresco, 1976a), and in the codon-anticodon interaction (Topal & Fresco, 1976b); and, how much do the facts concerning pairing favor (if at all) the second theory?
5. Does the fact that only the L-amino acids participate in the genetic code favor "The Stereochemical Theory" or not, especially if it can be shown that every codon fulfills the stereochemical conditions for coding the appropriate *L,S-dimer* (Grafstein, 1983, p 157: "An intricately coupled stereochemistry is formulated which displays a binary logic for amino acid-codon recognition")?
6. With the formulation of "the general base-pairing hypothesis" (Topal & Fresco, 1976a) and "the two out of three" hypothesis (Lagerkvist, 1978 and Lagerkvist et al., 1981) has the "Wobble Hypothesis" (Crick, 1966b) been refuted?
7. Has the genetic code been "from the beginning" as it is today: a four-letter alphabet (four amino-imino bases: two purines and two pyrimidines, with at least one base- uracil- which is only an imino base)

from which three-letter words are generated; plus the twenty-letter alphabet (20 amino-imino acids, 19 amino acids and 1 imino acid) from which one-letter words are generated. Or, was the genetic code originally (in the beginning) a four-letter alphabet with two-letter words; or a two-letter alphabet (2 amino-imino bases, 1 pyrimidine and 1 purine) with doublets or with triplets; of course, in all cases, with the suitable (which?) number of amino acids (cf. Eck, 1963; Jukes, 1963, 1966, 1973, 1983; Yockey, 1977; Eigen & Schuster, 1979; Rowe & Trainor, 1983b)?

(Note: By "the beginning" of the genetic code we mean the origin of life anywhere in the universe; in the sense that, if there's a genetic code, there is life, and if no code exists, then no life exists.)

8. Is the fact that the present day code completely represents the realization of a mathematical model - the third class variations with the repetition from the set of four elements (Gamow, 1954) of great importance (Konopka & Brendel, 1983, p 472: "The theoretical possibility... is a result of the mathematical structure of the genetic code"), or it is not of great importance (Osawa et al., 1992, p 230: "The general pattern of the genetic code results from biochemical properties of nucleotides rather than from any mathematical formula")?
9. Which factors have determined the replacements of amino acids in proteins during the evolutionary process (Dayhoff, 1969, 1972-1978; King & Jukes, 1969; Doolittle, 1981, 1985; Doolittle & Kyte, 1982; Swanson, 1984; Frömmel and Holzhütter, 1985; Taylor, 1986; Prat et al., 1986)?
10. Does Darwin's theory of selection, as a nonrandom process, still hold for the macromolecular level, and for the level of genomes, or are we talking about a "non-Darwinian Evolution" (King & Jukes, 1969) as a random and drift process, and as an indirect result of the existence of neutral mutations (Kimura, 1968)?

With argumentation for one general and several separate hypotheses (bearing the status of working hypotheses), we will show in this study that the answers to the previously asked questions have to be affirmative (the declaration of the position taken in the first part of the question section), except for the third and sixth question; the ninth question will be discussed separately.

## 2. THE HYPOTHETICAL FRAMEWORKS

2.1. *The general hypothesis:* Boolean (logical) spaces are the main determinants and the invariants of the genetic code.

2.2. *The separate hypotheses:*

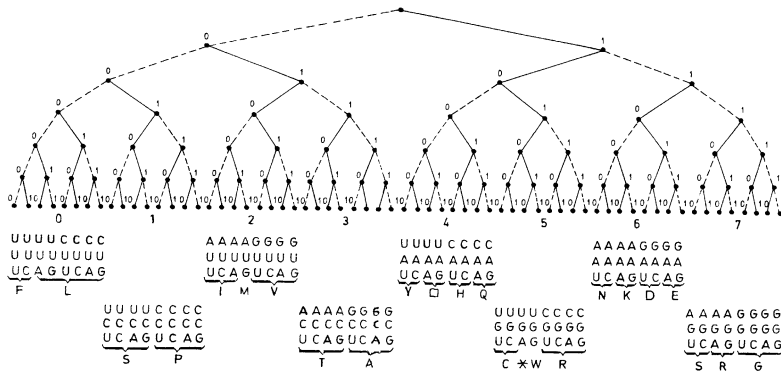
- 1) In answer to the question of whether there is any sense in talking about the evolution of the genetic code, a reliable answer can be found on condition that the following three *input-output* relations are correctly analyzed: I. *Input:* Codon-Anticodon interaction - *Output:* Codon - Amino acid relation; II. *Input:* Codon ring - *Output:* Mutation ring (both rings as in Swanson, 1984, p 188 and p 191; cf Appendix 1) and III. *Input:* Essential amino acids - *Output:* essential, semi-essential and non-essential amino acids;
- 2) *The wobble principle* is a universally - held principle for the genetic code and does not amount to only codon-anticodon interaction (Crick, 1966b);
- 3) The relation of *Strong - Middle (mixed) - Weak (SMW)* (Lagerkvist et al., 1981), that is, *Full-Semi - Empty (FSE)* (Rakoëvia, 1994) is a universally - held relation for the genetic code;
- 4) "*The Crossing - over*" principle is a universally - held principle for the genetic code not only for its physical but also for its logical systems (structures).

The presented argumentation for the stated hypotheses proves that the genetic code represents a whole, unique, and unified system with strict relations of binary symmetry, proportionality and harmoniousness of all its parts (constituents) within the whole; and that not only from the formal aspect (the number of molecules, atoms and nucleons) but also from the essential aspect (the structure and the physical and chemical properties of the constituents). The genetic code must have been in "the beginning" in the same state as it is at present (today) because the generation of such a genetic code is a prerequisite for the origin of life anywhere in the universe. (The chemical evolution of macromolecules, which occurred prior to the genesis of the genetic code, will be considered as being prebiotic in this study; cf Dickerson, 1978, pp 70-86: "One of the fascinating side issues of origin-of-life biochemistry is why the present set of 20 amino acids was chosen"; cf also Pflug, 1984, p 67: "A prebiotic evolution took place on the early earth. The origin of life is open to alternative explanations, including extraterrestrial phenomena").

**Remark 2.1.** All the three elementary types of symmetries (1. in relation to the point, i.e. center, 2. in relation to the line or axis and 3. in relation to the plane) can be represented by the binary symmetry of the segment line, i.e. by the symmetry of the entities  $A \leftrightarrow A'$  (or  $A \leftrightarrow B$ ) in relation to the central entity  $C$  - the center of symmetry (whether or not it exists, represented only by a point), where  $AC = CA' = n$  and  $AA' = 2n$ . If so, then:

The entity  $C$  contains (in itself) the quantity  $c$  ( $c = n$ ), which represents the arithmetical mean for  $AC$  and  $CA'$ . This is the essence of binary symmetry as the "symmetry in the simplest case"(Marcus, 1989, p 103: "In its simplest form, in a one-dimensional Euclidean space, symmetry is defined with respect to one point. Given two points  $A$  and  $B$  in this space, the symmetric point  $C$  of  $A$  with respect to  $B$  is one such that the distance from  $C$  to  $B$  is equal to the distance from  $A$  to  $B$ , whereas the distance from  $C$  to  $A$  is the sum of these two distances"; Notice that our  $B$  or  $A'$  is Marcus'  $C$  and vice versa). Its simplicity is the reason why we can consider binary symmetry as the best possible symmetry.

1. There is also the entity  $M$  which contains (in itself) the quantity  $m$ , where  $m = 4/3 n$ , which represents the harmonic mean for  $AC$  and  $AA'$  (the essence of binary harmony!);  
 $AA'$  can be, in infinitely numerous ways, divided into two unequal parts;  
 $AA'$  can, in a finite number of ways, be divided into two parts which are proportional to each other (the essence of binary proportionality!);
5. There is exactly one of pair of points  $G, G'$  which represent the *golden section* along the segment line  $AA'$  (the essence of infinite division and the best possible proportion!).



**Figure 1** The binary tree of the genetic code. It generates from the Gray code model of the genetic code (Swanson, 1984) by codons arranging according to the natural numbers series "for the numbers 0-63". The 8 rosettes on the binary tree correspond to 8 codon classes. The broken line is the primary (source) line and the full line is the secondary one; pyrimidine type molecule is the parent molecule while the purine type is its derivative. However, when the purine type is to be selected, it is the primary line for the purine type base but only in one step. The Arabic numerals, as the vector numbers designate the rosettes (classes) of codons that correspond to the vertices of the unit Boolean 3-cube.

**Remark 2.2.** The binary symmetry  $A \leftrightarrow A'$  (or  $A \leftrightarrow B$ ) in this paper is still understood, except by S. Marcus, in the sense used by P. Hilton and J. Pederson (1989, pp 73-74) so that the given entity from the pair  $A, A'$  (or  $A, B$ ) “may admit several different combinatorial structures and each structure will be regarded as combinatorially distinct. You should thus be warned that [entities] which we regard as *the same* (i.e. combinatorially equivalent), you may hitherto have regarded as *different* (see Fig.1(a)); and [entities] which we regard as different (i.e.combinatorially distinct), you may hitherto have regarded as the same (see Fig.1(b)).” For a better understanding of this we present a possible correspondence between their Fig.1 and our Fig.1. The entity on the left side of their Fig.1(a) - “the cube” - corresponds to the pyrimidine entity (in 32 combinations, or to be more correct, variations) on the left branch of the binary tree in our Fig.1; their right side entity (“the prism”) corresponds to our purine entity on the right side (also in 32 variations). The entity on the left side of any one of the 4+4 “rossete” (or classes) codons on the binary tree in our Fig.1 corresponds to their left entity in their Figure 1(b); a simpler cube model corresponds to our simpler pyrimidine (U) and/or purine (A) entity; their right entity - a more complex cube model - corresponds to our more complex pyrimidine (C) and/or purine (G) entity on the right side (cf analogous “cubes” and “prismes” in Fig. 3.5 in Dubinin, 1985, p 81).

**Remark 2.3.** Since the genetic code can be reduced to the Gray code model (Fig.1 in Swanson, 1984,p 188) and to a binary tree (Fig.1 in this paper), with a starting codon UUU 000000 and a final codon GGG 111111, it follows that as to questions of symmetry in relation to the genetic code *the mathematical group theory* holds only partially (our hypothesis and a prediction of this - *Prediction 1* - remains for further, that is, future research). This results from the fact that set Q of rational numbers, including zero, does not form *a group* with respect to a multiplication operation. The above mentioned is the reason why we won't use the mathematical group theory to research the symmetries of the genetic code in this paper.

### 3. GENETIC CODE AS A BOOLEAN SPACE

A more detailed analysis of (experimental) facts shows that the nature of the genetic code is such that the two contradictory views stated in the 8-th question in the *Introduction* hold true simultaneously: for the characteristics of the genetic code, which, being as they are, are “the result of the mathematical structure”, in other words, they are not that, they didn't originate “from any mathematical formula” but are the result of the “biochemical properties of nucleotides”. The genetic code, in fact, represents a unity of both one and the other: the relations of the characteristics of the genetic code are such that they correspond to an ideal (one or more) mathematical model; “correspond” in the sense that they are correspondent of and in accordance with the model.

## 4. GENETIC CODE NUCLEON NUMBER

Besides the strict, above-shown regularities of the genetic code, regularities characterize the genetic code in other ways as well. If codon systematization is observed not only in quartets but also in octets (Rumer,1966) we get exactly two classes of separate binary symmetrical codon doublets (the first and second base of the codon), the first class being within the first octet, and the second class within the second octet (Table 1 in Shcherbak,1989, p 272). The ratio of the number of doublets is 1:1 (or 8:8); which also corresponds to the number of codons in the two classes: 1:1 (32:32). As to the codon-coded entities (for amino acids and/or for termination entity), the ratio of four-codon and non-four-codon entities is 1:2 (that is, 8:16). Finally, the relation of the number of "strong" (C,G) to the number of "weak" bases (U,A) in codon doublets of the first octet is that of 3:1, whereas that relation in the second octet is 1:3.

### 4.1. Union of Chemistry, Physics and Boolean Arithmetic

However, what is in a way unexpected and most surprising is the fact that (binary) symmetry and proportionality is achieved through the number of nucleons (Fig. 1 in Shcherbak, 1994, p 475). Namely, from the aspect of nucleon number, 16 of the non-four-codon entities are symmetrically separated into the "head" and the "body" (the side chain) in one way, and the 8 four-codon entities in another. The first way "uses the same symbols", and the second way has "the numbers arranged by cyclic permutation", but in both cases the numbers in question are those taken from the table of the multiples of the number 037, which form a system arranged in accordance with module 9 (Table 1 in Shcherbak, 1994, p 476). The relation of the number of nucleons in the "heads" and "bodies" of non-four-codon entities is that of 1:1 (that is, 1110:1110), whereas the relation of the whole (molecule) to that of one of its individual parts "heads" and "bodies" is 2:1. On the other hand, the relation of the number of nucleons in the "heads" to that of the "bodies" of the four-codon entities (amino acids only!) is 16:9; that is, when the wholeness of the molecule is taken into account, proportionality is then reduced to very small numbers, not to any number, but to those numbers which demonstrate the squares of the first three Pythagorean numbers  $3^2:4^2:5^2$ . (*Hint*. Not only the total amino acid nucleon number, but also the total *pu-pyr* nucleon number is related to the multiples of 037; cf footnote in Shcherbak,1994, p 476).

## 5. HIERARCHY OF BOOLEAN SPACES

When the Watson-Crick table was first presented in the form of a codon cube (Fig. 64 in Eigen & Schuster, 1979), it was not possible then to expect anything in the way of a reality-model, much less the Boolean cube  $B^3$ . However, with the presentation of the "codon path cube" (Fig. 2 in Swanson, 1984, p 189) there was no doubt about it, all the more so since out of six possible choices in the Gray code model ( $B^6$ ), the situation is exactly balanced with the generation of  $B^3$ : the second base was chosen with both questions being taken into account (base type and number of hydrogen bonds) and the first base was chosen with the first question being considered (base type). Choosing, and doing so on the basis of only one question, means to choose! Choosing the first and second base and not the third, is a strict rule which can be otherwise expressed as choice according to the model of "two out of three" (cf. with the reading "two out of three" in the codon-anticodon system in Lagerkvist, 1978 and Lagerkvist et al., 1981). Knowing that, in the coding process according to the Watson-Crick Table, *mutatis mutandis*, only the first two bases are coding, and the third is noncoding (Lewin, 1987, p 129: "The pattern of third base degeneracy... shows that in almost all cases either the third base is irrelevant or a distinction is made only between purines and pyrimidines."), we can say that the choice according to the "two out of three" model is such that we are talking about a reality-model; therefore, the generated Boolean cube  $B^3$  (generated after the third choice) is also a reality-model. The relations of codon entities and amino acid entities in such a model are in fact shown in the genetic code binary tree (Fig. 1).

The achieved balance after the third choice is one in the sense that besides the number of chosen bases there were exactly the same number of those which were not chosen. The second base based on both questions and the first base based on one question were chosen; but the first base with one question and the third base with two questions were not. It is important to notice that at the realization of the six choices the first and second base are chosen by the essential presence of "crossing-over", whereas the choice of the third base takes place without it (Swanson, 1984, p 188: "Note the interleaving of the Gray code bits representing the first and second bases of codon.").

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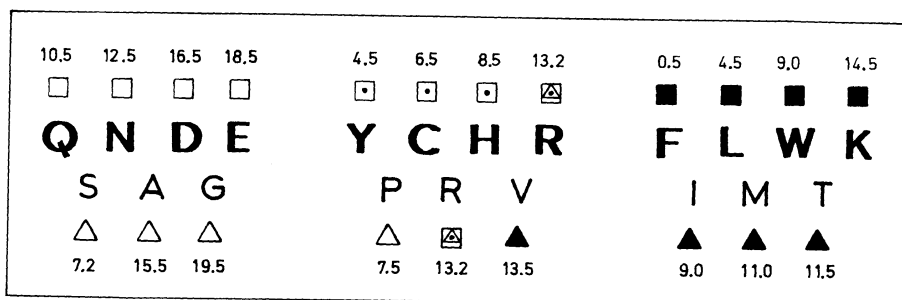
However, the "*two out of three*" and the "*crossing-over*" principles are fully observed with the fourth choice: the first two bases are then fully chosen, while the third base in the codon is not. This is the reason why the genetic code binary tree (Fig. 1), that is, the Gray code model (Fig.1 in Swanson, 1984, p 188) represents the unity of the Boolean cube and the hypercube  $B^3 - B^4$ . In accordance with this, it is understood that besides the eight large rosettes in the genetic code binary tree (0-7), there simultaneously exists 16 small rosettes (0-15).

## 6. PARAMETRIC RELATIONS

The informed reader will find it easier to see a hypercube in the binary tree (Fig. 1) than a cube, but the physical and chemical parameters, nevertheless, give priority to the cube. If the whole Boolean space of the cube is divided into two equal (and symmetrical) parts, into space-3 and space-4 (a harmonious division in the sense of the discussion given in chapter 3.3.), we will get two classes of amino acids (*Note*: Vertex 3 and adjoining vertices 1,2 and 7 form space-3; vertex 4 and adjoining vertices 0,5 and 6 form space-4.). Space-3 contains 9 amino acids: T,A; S,P; I,M,V; **R**,G. Space-4 contains 12 amino acids: Y,H,Q; F,L; C,W,**R**; N,K,D,E. Because the amino acid **R** appears in both spaces, the number of amino acids "increases" by 1 so that now there are "21 amino acids".

### 6.1. The Three Rings

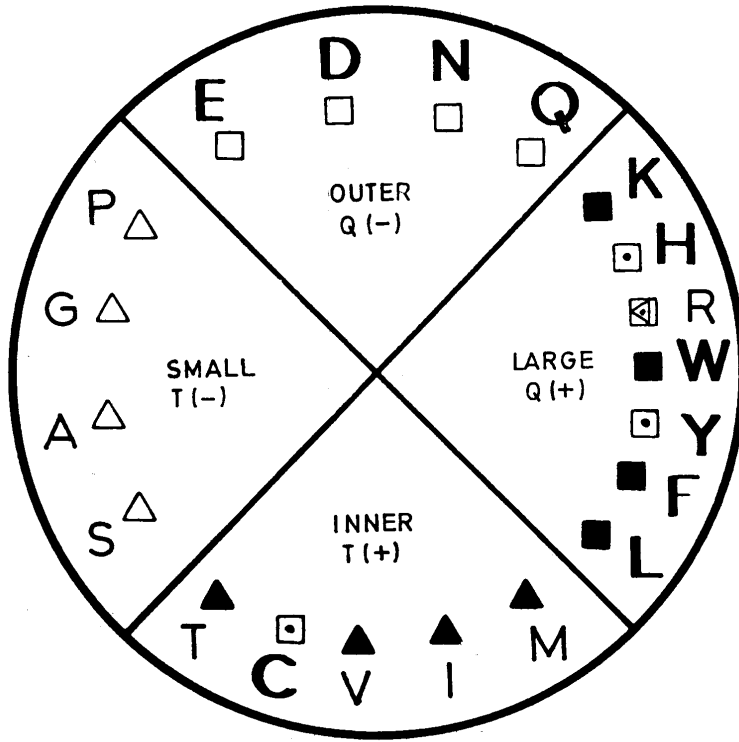
With division of the amino acids into two classes within Space-3 and Space-4 the existence of the physical properties ring, along with those of the Mutation ring and the Codon ring (Figs. 4,3,1 respectively, in Swanson, 1984) becomes evidently clear. If, in Figure 2 (Fig. 4 taken from Swanson, 1984, p 192) through the arc which passes through the points P-M and the arc which passes through the points D-F we divide the space into two parts - the right and left - then in the upper left part or in its adjoining area can be found amino acids from Space-3 (G,A,S,T,P), whereas amino acids from Space-4 (D,N,E,Q,K,R,H,Y,W) can be found in the upper right part or its adjoining area. After this division, in the lower part of the ring (far from the top part and its adjoining area) remain amino acids which are located exactly on the two arcs .....



**Figure 5(II)** Here are given amino acids from Space-3 and Space-4 as in previous Figure but here are taken the collective binary values (cf Rakočevia, 1980, p 10). In case of nonexistence of such values, the categorization (3 x 3) would not make any sense for Space-3, but only the categorization (2 x 4). Note that the sequences (Q, N, D, E) and (S, A, G, P) are the same as in Mutation ring.

With this we have total and definitive proof for the existence of the *Input* (Essential amino acids) - *Output* (Essential, semiessential and non-essential amino acids) relation presented in the second working hypothesis (Chapter 2). Of course, here it is understood that, for organisms which first came into being, all the amino acids had to be essential (in other words, non-essential, depending on the view; they were non-essential in the sense that the organisms themselves were able to synthesize all of them).

It is important to notice that with the systemization of amino acids, as given in Figure 5, the problem of amino acid classification is solved, and from the aspect of essentiality, that has been achieved according to the model 10 : 10 or the model 8 : 4 : 8 (4 semiessential amino acids). The surprisingly large number of different views about this problem, which we have mentioned in a previous study (Rakočevia, 1994, pp 84-85) now acquires a simple solution: amino acids must first of all separate into those of Space-3 and Space-4; only then can their essentiality be analyzed.



**Figure 6** Mutation ring II. This Ring could be regarded the Mutation ring II provided that R. Swanson's Mutation Ring (Swanson, 1984, Fig. 2) is regarded the Mutation Ring I; Everything is the same as on Mutation Ring I, only the S.T.-Q.K. line is shifted by one step on both ends in relation to Mutation Ring I; and P.E.-M.L. line is shifted only on one (the other) end. The squares designate the amino acids from Space-4 and triangles designate the amino acids from Space-3. The empty squares and empty triangles designate the nonessential amino acids, otherwise they designate the essential amino acids; the dots designate the semi-essential amino acids. The lines strictly separate non-essential from yes-essential amino acids; then the lines strictly separate the Space-3 amino acids from Space-4 amino acids. There are the two exceptions: C is full-strayed; R is semi-strayed. One should note that the complementarity principle is applied as follows: outer-inner: non-essential amino acids from Space-4 are complementary with the essential amino acids from Space-3, etc.

Surprises, however, do not stop here. We can see in Figure 6 how the arranged system of essential amino acids, determined by Space-3 and Space-4, brings order to the relations among the amino acids within the mutation ring. The essentiality of amino acids and the relation between Space-3 and Space-4, in fact, reveals that the Mutation ring (Fig. 3 in Swanson, 1984, p 191 - Mutation ring I) must exist in yet another form, as

shown in Fig. 6 in this paper (Mutation ring II). It should be noted that in the half of the ring with the non-essential amino acids there is no "Crossing-over", whereas in the half with the essential amino acids the "Crossing-over" exists: *full* (strong) "Crossing-over" for C, *semi* (middle) "Crossing-over" for R (and *empty* "Crossing-over" for other amino acids.). Binary symmetry is evident and so is proportionality: yes-essential: non-essential = 3:2 (or 12:8); non-essential from Space-3: non-essential from Space-4 = 1:1 (or 4:4); yes-essential from Space-4 (including R): yes-essential from Space-3 (excluding R) = 2:1 (or 8:4). Including and excluding the amino acid R is also another specific way of "Crossing-over".

With such a view regarding the structure of the mutation ring, we can be certain that it is the result of *a representative sample* not only from the aspect of the number of analyzed proteins, but also from the aspect of an a long enough passage of time in the process of evolution (Dayhoff, 1969; 1972-1978; Swanson, 1984). Bearing this knowledge in mind, it follows that in the *input* (codon ring) - *output* (mutation ring) relation, *feedback* had to exist, and had to be negative. But what does that practically mean? It means that with a sufficiently large number of "dice throws" (the replacement of amino acids in proteins as a result of mutations), the relations among the amino acids in the proteins have come to be the same as those originally found in the genetic code. There is, therefore, no discontinuation, which means that the genetic code was originally the same as it is today. Mutations, even when they are "obviously" neutral in fact are not neutral. All of them are an indispensable part of the whole, representing at least the smallest pebble which are, one by one, continually and gradually built into the mosaic, which after a long enough time forms in such a way as to be the exact copy of the mosaic originally contained in the genetic code itself. If all this is so (and this follows from the analyzed results), then we have a full and definitive proof for the existence of a Codon ring (*Input*) - Mutation ring (*Output*) relation (First working hypothesis in chapter 2); then not even the Non-Darwinian evolution existed, being that it was based on wrong suppositions about the possibilities of neutrality for mutations. With this the answer to question 10 from the *Introduction* has been given.

With accurately argued proof that Boolean spaces are actually the main determinants and invariants of the genetic code, then non-Darwinian evolution, *per se*, is not possible. However, independently of this, in the very act of founding the theory of non-Darwinian evolution many methodological mistakes have been made. The main experimental result on which the findings of this theory has been based (Figure 1 and Table 6 in

King & Jukes, 1969, p 796) originated from a *selective*, instead of a *representative* sample ("53 completely sequenced *mammalian* proteins") (*italics* M.R.). On the other hand, basing their theory on the genetic essence of being, the authors of the mentioned theory, have again made a mistake. They have started from both the genotype and the phenotype model, that is, from two entities of the genetic essence of being, as defined by Johannsen (1909, 1913), and which are in their sense non-reality models or conventions; instead of starting from reality-models, as perceived and defined by Mendel (1866) and who have reduced the entity number to two instead of four, with a strict mathematical interdependence: Stammarten - Konstante Formen - Glieder - Individuen,  $1^n - 2^n - 3^n - 4^n$ , respectively. In other words, using modern terminology, we can say the following: Parent type - Phenotype - Genotype - Individual type (see Rako~evi}, 1994, pp175-177 for details).

## 6.2. Codon-Anticodon and Codon-Amino Acid Relations

The results, which we are presenting above in so straightforward a manner, are also strengthened by the results given in Table 1. The relations among the amino acids given in this Table are, in fact, "copied" relations of the amino acids united in the Codon ring - Mutation ring system (*see* Appendix 1). As we can see, the amino acids are strictly divided on the basis of the "key" of positive and negative values of a very important parameter, that of hydropathy (Doolittle & Kyte, 1982).

The presented conclusion may be surprising for the reader because it has been drawn only from the relation (and interaction) of codons - amino acids (cf Reuben & Plok, 1980, p 111: "The genetic code appears be the 'fossil record' of nucleotide - amino acid interactions in the prebiotic milieu"). At first sight it seems as if the codons - anticodons interactions have not been taken into consideration at all. The contradiction, however, disappears when the following two things are understood:

## 7. FINAL COMMENTS

How has the genetic code become "from the beginning" that what it was: why with those bases and that exact number of bases; why with those amino acids and why with that exact number of amino acids; with exactly 3 "stop" codons in the alphabet which functions on the level of words, with exactly one termination situation in the alphabet which functions on the level of letters (as showed graphically in Figure 1 in Shcherbak, 1994, p 475)? All this follows from a strict determination by nucleon number presented in chapter 4 and a strict determination based on physical and chemical parameters presented in chapter 6. The genetic code, therefore, must be universal for life which could exist anywhere in the universe (with this the answer to question 1 from the *Introduction* has been given). But it is not universal in the sense that there is one-meaning correspondence between the words of one alphabet and the letters of the other alphabet in all cases. On the contrary, for the largest number of cases the correspondence is really one of one-meaning (*strong*), but in a number of cases there must be a deviation from one-meaning, and that by two possible levels: *middle* and *weak*. In a previous work (Rakoëviæ, 1988, pp 182-183), we have given the following prediction: "the optimal path in the process of coding (insofar as there aren't any anomalies) is realized with at least one binary step and at the most with two! Therefore, all exceptions from the universal code can appear only within these limits... The phenomenon of multiple-meanings in cases of suppression does not overstep the limits of the two binary steps." And now we can more precisely say: the deviation ("*wobble*" or "*wobbling*") from one-meaning in the coding process is a law, a universal principle, and in the case of the genetic code this principle manifests itself in such a way that there are "one-meaning" limits which is *strong* (in most cases), then a "one-meaning" which is slightly weaker (within the limits of one bit in the Gray code model, or in the genetic code binary tree), *middle*, and an even weaker "one-meaning" (within the limits of two bits), "*weak*" (with this the answer to question 2 from the *Introduction* has been given).

All examples of deviations from the standard genetic code, presented prior to or following 1988, confirm our prediction: they are deviations only within the limits of two bits. We should, however, list some concrete examples: Kuchino et al. (1985) and Horowitz & Gorovskiy (1985) report that in *the Tetrahymena thermophily* codon UAA there is no "stop"

meaning, but it codes for glutamine. The UAA position in the standard code binary tree is determined by means of the Boolean vector (100010). The position of the first codon which codes for glutamine of codon CAA is (100110). The difference is 1 bit. The position of the second codon, CAG, is (100111). As we can see, the difference is two bits (the difference in the number of ones). And now the conclusion: from the aspect of the first codon, the situation in the change of one-meaning can be described as *middle*, and from the aspect of the second codon, as *weak*; in relation to both codons, the situation is, however, *mixed*. Osawa et al. (1992, p 230) report, however, that "in certain ciliated protozoans, UAR codes for Gln." This means that, besides UAA, UAG codes for Gln. In either case, the limit of two bits is not violated (the reader can easily convince himself of that by "reading" the six-bit-records of appropriate codons in the binary tree in Figure 1). The second example, as reported by Yamao et al. (1985, p 2306) and Osawa et al. (1992, p 230), refers to the organism *Mycoplasma capricolum* in which "UGA codes for Trp." But, instead of citing examples of particular cases, we can generally conclude the following: in all cases of deviation from the standard code, which have been discussed by a great number of researchers (Sanger et al., 1981; Jukes, 1983; Attardi, 1985; Alvager et al., 1989; Osawa et al., 1992), are such that they do not violate the limit of two bits. With this, our prediction from 1988 forward still holds (now as *Prediction 7*): and in the future there will not appear cases of deviation from the standard code by more than two bits.

The discussed cases of deviation from one-meaning given by the standard code concern homonymy (one and the same codon has different meanings in different systems). However, deviations from one-meaning are determined by the *strong-middle-weak* relation even when the chemical composition of the genetic code constituents (amino-imino acids and amino-imino bases) are considered. The 18 amino acids are strictly one-meaning, in the sense that all are made up from the same 4 kinds of atoms - H, C, N, O. They, therefore, have a *strong* one-meaning. For the remaining 2 amino acids (M & C) a deviation ("*wobble*" or "*wobbling*") already appears, and so does the fifth kind of atom (S); this is how "weakening" of one-meaning occurs. In regard to that, methionine (in both forms: sulpho-methionine and seleno-methionine) stays *middle*, while cysteine "weakens" even further to become *weak*. It becomes so in two ways. First, it "multiplies" itself for a whole "step", that is, for one whole "neighborhood" - in proteins it appears in the form of cystine. Secondly, it becomes "weak" by "multiplying" its standard nucleus (atom S) by one whole neighborhood (Se) (by one electron

level!), so that it gives rise to a "nonstandard nucleus" (atom Se) and with it, to amino acid selenosysteine (cf. Voet & Voet, 1990, p 912; Osawa et al., 1992, p 254; cf. "The anomalous" behavior of cysteine in Mutation ring II in Figure 6.).

(Osawa et al., 1992, p 254: "One of the most remarkable properties of coding is the occasional incorporation of selenocysteine in polypeptide synthesis in both prokaryotes and vertebrates. Secys has been sometimes termed the '21st amino acid'. It occurs as the active center of a few enzymes... Enzymes containing Secys have not been detected in green plants"; and further at the same page: "Notably, Secys cannot replace cysteine in cysteine tRNA. In this respect, Secys is unlike selenomethionine, which can become aminoacylated to methionine tRNA and is then incorporated into thiolase of *Clostridium kluyveri*");

Our prediction for future research (*Prediction 8*) is that an analogous strict determination of one-meaning - multiple-meanings has to exist for amino-imino bases as well, whose determination we can now only hint at. Namely, in the following sense: from the aspect of "standardization", C, A, G have a "strong" one-meaning, while T and U already show a "weakening" - the next step in the "weakening" is represented by different modifications of nonstandard pyrimidine and purine bases (cf. Voet & Voet, pp 902-903).

Strict determination of one-meaning - multiple-meanings of amino acids by way of the *strong-weak-middle (mixed)* relation is important for the pairing and non-pairing of amino acids from the aspect of their stereochemical categorization (cf chapter 4.1.). If it is noticeable that according to the character of the influence of the side chain R on the conformational freedom of the basic mono-peptide segment (-CONH - C<sup>α</sup>HR - CONH -), the 20 canonical amino acids can be categorized into 4 stereochemical types: *Gly*, *Ala*, *Val*, and *Pro* (Popov, 1989, p 79), determination then takes place in the following manner. According to E.M.Popov, glycine belongs to type *Gly*, proline belongs to only type *Pro*, Isoleucine, together with valine, belongs to type *Val*, while the remaining 15 (of the total 16) amino acids belong to type *Ala*. Bearing this in mind, we are of the opinion that every chemist can easily see that the 16 amino acids of the *Ala* type are strictly divided into 8 pairs: A-L, S-T, C-M, N-Q, D-E, K-R, H-W, and F-Y. The following conclusion can be drawn from this: from the aspect of strict stereochemical one-meaning pairing (*strong*), there is only one pair of amino acids, and that is V-I; one pair is *weak (empty)*, but it is not really a pair: G-P; finally, then all the remaining 8 pairs within the stereochemical type *Ala*, are *mixed*, in the sense that it has 8 different

variations of one and the same stereochemical type. If we add to this the fact that stereochemical pairing - non-pairing is determined, also very strictly, by the number of nucleons, and even by perfect numbers (cf. Appendix 3), then no special discussion is necessary to additionally prove why "The Stereochemical Theory", and not "The Frozen Accident Theory" holds true for the genetic code (with this the answers to question 4-5 from the *Introduction* have been given). Moreover, it becomes obviously clear why the genetic code had to be "from the beginning" the same as it is today (with this the answers to question 7 from the *Introduction* have been given).

When it is once perceived and understood that the Boolean spaces are the main determinants and invariants of the genetic code, as we have shown in the previous six chapters, then all the other experimental results as to the genetic code have to be perceived in a different light and differently interpreted. We will show this with several examples. It follows from the accurately given "Mutation Data Matrix", MDM, (Dayhoff et al., 1979; Dayhoff & Orcutt, 1985) that the evolution of proteins was "a random" process (no ordering of amino acid groups in the matrix is perceivable). But that is, in fact, due to the fact that the order of amino acids is not the one that would unavoidably follow from the positions of amino acids in the Boolean space. With such an order, the situation is the opposite (as expected!): a strict ordering by amino acid group exists; in other words, the evolution of proteins must be "a non-random" process (cf. the original order of amino acids in the MDM with our order in Rakoëvi, 1988, p 196 and 197; the table on p 196 is the same one from Figure 4 on p 7 in Dayhoff & Orcutt, 1985). The same holds for "The genetic code matrix" (Dayhoff et al., 1979; Dayhoff & Orcutt, 1985): in the original order of the amino acids, there are as many as 12 mismatchings (the mismatching of number 3 with number 2 along the diagonal, whereas in our order there are only 4 mismatchings (cf. Table on p 193 and Table on p 195 in Rakoëvi, 1988). Of course, in our original matrix, which strictly follows the position of amino acids in the Boolean space, there is not even one mismatching (Table 48 in Rakoëvi, 1988, p 192). (*Note.* Table 49 in our study on p 193 is the same one from Figure 3 in Dayhoff & Orcutt, 1985, p 6. The necessity of matching of numbers 3 and 2 is clear from the explanation given by Dayhoff & Orcutt, 1985, p 6: "Identical amino acids obtain a score of 3; those for which two nucleotides could be identical, 2; one nucleotide, 1; and 0 if no nucleotides are ever shared in the codons for the amino acids").

The presented "genetic code matrix" can also exist in its inverse form which was used by Fitch & Margoliash (1967, p 280) and Leunissen & De

Jong (1986, p 192). In such a case, “the table is symmetrical about the diagonal of zeros.” In any case, there still remains 12 mismatches in it. However, altered by our (Boolean) order of amino acids (Rakoëviæ, 1988, p 180) there are no more than 5 mismatches. Undoubtedly, our original (Boolean) matrix even in this form shows not even one mismatching (Rakoëviæ, 1988, p 188). There is no need to specifically emphasize the fact that the results of the previously mentioned authors, which follow from the comparisons with “the genetic code matrix”, would have been different had that matrix had the Boolean order of amino acids.

Instead of every researcher having to give his order of amino acids in the mutation matrix, or in the matrix of the genetic code, it is essential that the order be standardized, and that, only that order which follows from the positions of the amino acids within the Boolean spaces, with respect to “the unit change law”, that is, the allowed change should vary only by one bit going from one amino acid to the next in the genetic code binary tree (Figure 1), perceived as being three-dimensional (three-four-dimensional to be more exact).

Schulz and Schirmer (1979, p 172) changed the order of amino acids in “the Mutation probability matrix for the evolutionary distance of 2 PAM’s” (Dayhoff, 1972, p 92), with the aim of explaining the main result on which the “Non-Darwinian Evolution” theory was based (King & Jukes, 1969). Had they brought the change to its end (reduced it to the Boolean order), their observations would have been more complete, but as it is, because of the good correspondence of their order to the Boolean one, their observations are exceptional. Contrary to the conclusion of King & Jukes, they hold that the result as to “correlation between observed and expected amino acid frequency” (p 173) favors Darwin’s Theory of Selection, and not the other way around (p 174: “Therefore it cannot be deduced from the correlation between such summary values as amino acid frequencies that the evolution is neutral, i.e., non-Darwinian”) (cf. Rakoëviæ, 1988, p 72: “From the experimental results we will here cite those of King and Jukes... In spite of the fact that these authors are using this result to refute Darwinism, facts are facts, and the question of scientific conclusion depends at times on the subject himself - the scientist”).

The complete analysis we have given in this paper confirms that the frequencies expected on the basis of the genetic code cannot at all be random, but are (with the representative sample, not only from the aspect of a sufficiently long evolution period, but also from the aspect of a sufficient number of different kinds of organisms taken for analysis) evidently non-

random. With the correct conclusion, therefore, the result of King and Jukes is excellent because it shows that, in spite of the small selective sample (p 796: “Graph showing the similarity between the observed frequencies of amino acids in 53 completely sequenced mammalian proteins”), the *output* is such as expected on the basis of the *input* - the physical and chemical properties of the genetic code constituents and their positions within Boolean space. That this is indeed so is also proven by “the Growth factor for 2 PAM” which was presented by Schulz and Schirmer (Figure 9-1b, p 173), and which corresponds to the graph of King and Jukes. Schulz and Schirmer perceive the agreement but cannot make sense of it (p 174: “Note that no attempt was made to explain the observed correlation of Figure 9-1b”). And the sense is more than evident. The graph on (their) Figure 9-1b represents, in fact, the symmetrical order of the amino acids from Space-3 and Space-4 and that in the following way: below the line of the graph are the amino acids from Space-3: M, I, P T, S and R; above the line of the graph are the amino acids from Space-4: W, C, H, F, Y, D, K and L; with this another full Crossing over is realized: two amino acids from Space-3 have strayed into Space-4 (A,V), and two amino acids from Space-4 have strayed into Space-3 (N,Q); but a semi Crossing over is also realized: exactly on the line of the graph is one amino acid from Space-3 (G) and one from Space-4 (E). Thus, to conclude: from the aspect of Crossing over, (A,V) and (N,Q) are “full” (complete Crossing over); (G) and (E) are “semi” (semi Crossing over), whereas all the remaining amino acids are “empty” (there is no crossing over).

As to the strict agreement of experimental results with theory, for future research, the following important things must be kept in mind. Selective samples are permissible only in cases when the power and range of the *input* - *output* relation is examined (in the sense designated in the first working hypothesis in chapter 2), otherwise they are not permissible; they are especially not permissible regarding things which pertain to the question of the existence of a Darwinian or non-Darwinian evolution. In that sense, all criticism directed at King and Jukes by L. Gatlin in the all-embracing polemic is justified:

*King & Jukes (1969), p 789:* “As far as is known, synonymous mutations are truly neutral with respect to natural selection.”

*Gatlin (1972), p 198:* “This is not the case with respect to... selection”; p 180: “King and Jukes (1969) have selected an amino acid composition from a sample of vertebrate proteins which they believe is representative.” As to

further debateable aspects of this polemic, see appropriate numbers in *J. Mol. Evol.* (7, 185-195, 1976; 8, 295-297, 1976 and 8, 299-300, 1976).

One of the questions which was a rather polemical subject is "the conspicuous disparity of the observed and expected frequencies of occurrence for arginine" (King & Jukes, 1969, p 797). Not intending to spark off any discussions in regard to this, we will remind ourselves of the fact that arginine is the only amino acid which is simultaneously located in both spaces, Space-3 and Space-4, of the Boolean cube, bringing the number of amino acids to a total of "21". There is disparity there, and there is disparity here! And to top all surprises: this amino acid deviates from even this deviation - within Mutation ring II in Figure 6 this amino acid is located in only Space-4, and not in Space-3 as would be expected. All in all, we can see that the behaviour of this amino acid is characterized by a specific "wobbling" (existing to a significant degree). Therefore, in the system of 20 amino acids, it can certainly carry the epithet - "the wobbling of wobbling's wobbling" (I Wobbling: the genetic code, due to the fact that there exist deviations from the standard code within the limits of one and/or two bits; II wobbling: the 20 canonical amino acids, bearing in mind the fact that they can be "forced" to become "21" amino acids; III wobbling: arginine, by means of which this "forcing" is realized.). The reader here probably recalls that the next amino acid which can also carry this epithet is cysteine (see previous discussion and compare with position C and R in Mutation ring II in Figure 6; also notice that C is the only amino acid in the right half of the Watson-Crick Table which has a positive value for the hydrophathy index.)

What is in a way paradoxical, however, is the fact that if any of the 20 amino acids can carry the epithet - "the invariant of the invariant's invariant"- then that amino acid is arginine again. That follows from its position in the system in Figure 5. Without arginine that system would be neither symmetrical nor harmonious; and no other amino acid could replace arginine in that role, not even ornithine, despite Jukes' findings (Jukes, 1973, p 24: "I have suggested that arginine displaced ornithine during the evolution of protein synthesis"). Notice here that arginine has a very complex structure and that it is a semi-essential amino acid for most organisms; on the contrary, ornithine has a very simple structure, thus making it a non-essential amino acid (cf. Van Nostrand's Scient. Enc., 1983, p 119) (*Hint.* I invariant: the genetic code, the fact that it is universal, with the permissible 2 steps of freedom; II invariant: the 20 canonical amino acids, the fact being that from the genesis of the genetic code until the

present day, there have been 20 amino acids, as there will be in the future, despite the "wobbling" behaviour of arginine and cysteine; III invariant - arginine and/or cysteine, the fact being that without arginine the system in Figure 5 could not exist, and/or the fact that the role played by sulpho-cysteine and seleno-cysteine cannot be played by any other amino acid.).

It should also be noticed that the three "wobblings", i.e., the three invariants, can be "read" in the opposite direction where I becomes III and vice-versa. In that case, in the role of entity I can be found any one of the 20 amino acids with a precisely defined degree of "wobbling", that is, invariance.

Finally, it should also be noticed that everything that holds for the system of the 20 canonical amino acids analogously holds for the system of the four canonical bases (U, C, A, G) as well. This system can also be "forced", in other words, increased by exactly one base and which can be done in two ways. Accordingly, cysteine's analogue is uracil, whereas arginine's analogues are A and G simultaneously. Analogous to the "widening" of sulpho-cysteine into seleno-cysteine, uracil "widens" in the interaction of DNA-RNA (in the transcription process) in such a way that it becomes even thymine. On the other hand, the fact that what is happening to arginine is unreal ("mapping" two unreal entities from Space-3 and Space-4 in a real molecule of arginine), what happens to adenine and guanine is real: these two real entities are "mapping" themselves into a new real entity: hypoxanthine (primarily in the codon-anticodon interaction, in processes of translation. Besides all this, the system of "20 + 1" amino acids is "clean" (less "wobbling"), whereas the system of "4 + 1" bases in one way, and "4 + 1" bases in another way, in other words, the system of "4 + 1 + 1" bases, is "dirty" (more "wobbling") due to the existence of a great number of modifications. [*Hint*. A maximally widened system of "21" amino acids and a maximally widened system of 6 (4 + 2) bases, exist in a strictly harmonious relationship of the first (6) and the second (28) perfect number; in the sense that 21 is 3/4 of 28, and 6 is 4/4 of 6. The quantities 3 and 4 exist in the relation of the best possible harmony, as we have shown in many instances. Notice, in regard to this, that the quantities 3 and 4 are here connected by the mathematical operation of division, whereas in the system in Figure 5 they are connected by the operation of multiplication, which also represents a special kind of inversion. With this the sense of classification 8 : 4 : 8 in the system in Figure 5 becomes even more clear].

The strict agreement of theory and experimental research, as we have shown in the six chapters and the Discussion of this research paper,

demands other requirements. The Codon ring, Mutation ring I and Mutation ring II (as we have presented them in this paper), must be in the future used as standard and referential systems, in the sense that they are reality-models, and changes regarding them are not permissible. Not even minimal changes can be tolerated, like those carried out by Taylor (1986, p 208), who has changed the positions for H and R in the mutation ring; much less greater changes which, (for 8 amino acids) also in the mutation ring, observing it as “the rosette”, were carried out by A. Prat and her associates (1986, p 56, Figure 5) (the very idea of a “rosette” is otherwise an excellent one and it agrees with our own view of the eight rosettes in the binary tree, Figure 1).

On the basis of what we have presented, on the basis of the discussion given in every one of the six chapters, as well as all integral discussions, the inevitable conclusion is that all the working hypotheses given in chapter 2 have been proved. The general hypothesis, according to which the Boolean spaces are actually the main determinants and invariants of the genetic code, has been therefore proven. The Boolean spaces have been shown to be reality-models! From this it further follows that it makes no sense to talk about the neutrality of mutations, or about a non-Darwinian evolution.

In specific places in our paper answers were directly or indirectly given to all the questions mentioned in the *Introduction*, except for question number 3 and number 6, which were directly answered, through the evidence given for the four separate hypotheses. Thus, “the present status of Wobble usage” or “the general base-pairing hypothesis”, or “the two out of three” hypothesis, do not refute “the wobble hypothesis” but do, in fact, promote it to a generally-held principle for the genetic code. On the other hand, the genetic code, being redundant, did not become degenerate in the process of evolution, but was generated in origin as such. It is today as it was in the beginning and it will remain so in the future anywhere in the universe, because that follows from the positions of the bioelements in the periodic system of elements; bioelements - being the constituents of the genetic code. Accordingly, it makes no sense to talk about the evolution of the genetic code, but it does make sense to talk about the evolution of the macromolecules, that is, the evolution of life which came into being on the basis of just such a code - a universal genetic code.