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Ancient DNA sequence revealed by error-correcting codes

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A previously described DNA sequence generator algorithm (DNA-SGA) using error-correcting codes has been employed as a computational tool to address the evolutionary pathway of the genetic code. The code-generated sequence alignment demonstrated that a residue mutation revealed by the code can be found in the same position in sequences of distantly related taxa. Furthermore, the code-generated sequences do not promote amino acid changes in the deviant genomes through codon reassignment. A Bayesian evolutionary analysis of both code-generated and homologous sequences of the *Arabidopsis thaliana* malate dehydrogenase gene indicates an approximately 1 MYA divergence time from the MDH code-generated sequence node to its paralogous sequences. The DNA-SGA helps to determine the plesiomorphic state of DNA sequences because a single nucleotide alteration often occurs in distantly related taxa and can be found in the alternative codon patterns of noncanonical genetic codes. As a consequence, the algorithm may reveal an earlier stage of the evolution of the standard code.

Biological and digital communication systems have similarities with respect to the corresponding procedures used to convey the biological and digital information from one point to another, as well as in the data storage of digital media in a redundant array of independent disks (RAID)¹ and the storage of genetic information in chromosomes. These similarities enable the use of algorithms in the modeling and analyses of biological systems and data. For instance, in eukaryotic cells, the information contained in the DNA is transmitted through RNA to produce the proteins needed at a precise moment and in specific compartments in the cell. Many enzymes and complex molecules coordinate their transport and are often assisted by protein intermediates in the cytosol and organellar membranes, thus identifying the correct location of a protein. In the same way, the transmission of flawless data through noisy channels in digital communication systems can be reliably achieved if, in addition to using an error-correcting code (ECC), extensive signal processing techniques are also employed².

For quite some time there have been attempts to confirm the existence of an error-control mechanism in biological sequences similar to the ECC employed in digital sequences³, and although relevant, such studies have yet to provide a definitive answer. Recently our group developed an algorithm, known as DNA Sequence Generator Algorithm, which verifies whether a given DNA sequence can be identified as a codeword of an ECC. This goal was achieved when many distinct DNA sequences were identified as code words of G-linear codes (consisting of specific mappings and the underlying BCH codes)^{4–7} an important subclass of cyclic codes.

BCH codes were first proposed by Hocquenghem⁸ and independently rediscovered by Bose and Chaudhuri⁹; therefore, the acronym is made up of the initials of Bose, Chaudhuri, and Hocquenghem. When an underlying BCH code over Galois ring extension and/or Galois field extension identifies a given DNA sequence, two things may occur: 1) the given DNA sequence is a codeword of a G-linear

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code; or 2) it is a sequence belonging to the set of neighboring sequences differing by at least one nucleotide from the corresponding codeword of a G-linear code. This set of neighboring sequences is referred to as the “cloud” of a codeword.

When the DNA sequence generation algorithm identifies a DNA sequence belonging to the cloud of a codeword, it differs in a single nucleotide from the original sequence. Similar to biological DNA, this generated codeword may represent a silent mutation causing no effect on the translated amino acid or it may cause a residue change affecting for instance the protein structure and activity and consequently impairing its interactions with other proteins. Furthermore, the single nucleotide alteration can be restored, or equivalently, the codeword can be reverse engineered, returning it to its original sequence by applying one of the following algorithms: the Berlekamp-Massey decoding algorithm for codes over Galois field extensions^{10,11} or the Modified Berlekamp-Massey decoding algorithm for codes over Galois ring extensions^{12,13}, together with the corresponding labeling associated with each analyzed sequence.

Recently, Ivanova and colleagues¹⁴ used a metagenomics approach to survey the prevalence of stop codon reassignment in naturally occurring microbial populations and proposed that the canonical genetic code may contain some deviations. Similarly, studies of the evolution of the genetic code have developed a hypothesis that differs from a frozen universal code^{15–19} and even the universality of the code^{20,21}. It has been observed that each deviant genetic code contains codons that are associated with different amino acids and also with the canonical genetic code. Consequently, one may infer that such a process may have evolved from a standard code¹⁶. Such deviant genetic codes can be found in nuclear and mitochondrial genomes, in which mechanisms of codon reassignment have led to the differential reading of certain codons^{22–24}. The evolution of the genetic code plays an important role in understanding the differences between the response of the DNA sequence identification process and the given DNA sequence because these differences can be related to either the canonical genetic code or to the several deviant genetic code^{4–7,22}. In another example, Inomata and colleagues²⁵ using multiple sequence alignment and test of neutrality, have demonstrated that a single replacement of guanine with adenine (position 926 of the gene) in *Drosophila melanogaster*, resulting on threonine at the 218 - amino acid position, was the ancestral form of the Gr5a gene in *D. melanogaster*²⁵ and this single amino acid polymorphism (ALA218THR) represents a key impact on the trehalose sensitiveness.

The proposal of mathematical models describing such biological systems provides the needed tools for the development of systematic approaches for studies of mutations and polymorphisms and has applications in genetic engineering.

Thus, if an ECC can identify differences in a DNA sequence with a one-nucleotide resolution, the questions that should be addressed are as follows: if there is an error-correcting code underlying the DNA sequences, what are the biological implications regarding the single nucleotide (SNP) difference? And, is there a biological reasoning for such a difference? In the present study, we used the ECC approach proposed in references^{4–7} to evaluate whether the nucleotide difference between the original DNA sequence and the sequence identified as the codeword of the ECC is biologically significant in terms of evolution of this identified polymorphism.

Results and Discussion

In this study the DNA sequence generation algorithm was applied as a computational tool to provide strong evidence of the evolution of the genetic code, in special on nucleotide and amino acid site specific polymorphism, by showing the existence of a mathematical structure underlying the actual DNA sequences and by investigating the real biological meaning of the difference in the specific position pointed out by the code-generated sequences.

The code-generated sequences that had a single nucleotide alteration, causing a residue change in the translated protein, were used in a Blastx analysis to verify if the alteration suggested by the ECC could be found in other sequences.

Analyses were run for the code generated sequences of the *Saccharomyces* YMR193 gene (GI 45269853), the *Triticum aestivum* wPR4 gene (GI 78096542), the *Nicotiana tabacum* antifungal CBP 20 gene (GI 632733), the *Citrus sinensis* chlorophyllase gene (GI 7328566), the *Arabidopsis thaliana* hevein-like protein PR4 gene (GI 186509758), the *Saccharomyces cerevisiae* OXA gene (GI 832917) and the *Homo sapiens* F1F0 ATP-synthase gene (GI 12587). These sequences are shown in Table S01.

As a result of this search approach, a number of different genes were found to contain the same nucleotide at the same altered position suggested by the error-correcting code, see Tables 1 and S02.

In some of the results, the suggested polymorphism could be found in DNA sequences of taxa that were closely related to the query sequence. For example, for the code-generated sequence of the YMR 193 gene from *Saccharomyces cerevisiae* (Tables S02a and S02b), a mitochondrial protein involved in the large ribosomal subunit, the same residue was also found in other Ascomycota sequences. The results for the code-generated antifungal CPB 20 gene from *Nicotiana tabacum* were similar to those from other eudicots. The results for the chlorophyllase gene in *Citrus sinensis* were also found in sequences in *Populus* spp. And the code-generated sequence for the OXA gene, which is involved in cytochrome oxidase biogenesis in *Saccharomyces cerevisiae*, showed the same residue in the altered position in other ascomycete sequences. However, different cases were found as well, such as the F1F0 ATP-synthase gene from *Homo sapiens*, in which the code-generated polymorphism of His to Gln could only be found at the same position in certain fungi sequences, a very distantly related taxa to *H. sapiens*, which may

Tables	DNA sequences	GI number	Organism	L R-F	Primitive polynomial	Generator polynomial
S02.a)	TS	45269853	Sc	D/F	x^3+ax^2+bx+b	x^6+x^5+1
S02.b)	TS	45269853	Sc	B/R	$x^6+x^4+x^3+x+1$	$x^6+2x^5+x^4+x^3+3x+1$
S02.c)	TS*	78096542	Ts	D/F	x^3+bx^2+x+a	$x^6+x^5+x^4+x+1$
S02.d)	TS*	78096542	Ts	C/R	$x^6+x^5+x^4+x+1$	$x^6+x^5+x^4+2x^2+3x+1$
S02.e)	TS*	632733	Nt	A/R	$x^6+x^5+x^2+x+1$	$x^6+3x^5+2x^4+x^2+x+1$
S02.f)	TS*	632733	Nt	A/R	$x^6+x^5+x^3+x^2+1$	$x^6+3x^5+x^3+x^2+2x+1$
S02.g)	TS	7328566	Cs	B/R	x^6+x^5+1	$x^6+3x^5+2x^3+1$
S02.h)	TS*	186509758	At	A/R	$x^6+x^5+x^3+x^2+1$	$x^6+3x^5+x^3+x^2+2x+1$
S02.i)	PM	832917	Sc	A/R	$x^6+x^5+x^2+x+1$	$x^6+3x^5+2x^4+x^2+x+1$
S02.j)	TS	12587	Hs	C/R	x^6+x^5+1	$x^6+3x^5+2x^3+1$
2a and b	?	30695458	At	C/R	$x^{10}+x^9+x^8+x^7+x^6+x^4+x^3+x+1$	$x^{10}+x^9+x^8+3x^7+x^6+x^4+x^3+3x+1$
3.a)	TS	217937	Ib	B/R	x^3+ax^2+ax+a	$x^6+x^5+x^3+x^2+1$
3.b)	TS	51093376	Pd	D/F	x^3+ax^2+bx+b	x^6+x^5+1
3.c)	TS	16740522	Mm	A/R	$x^6+x^5+x^4+x+1$	$x^6+x^5+x^4+2x^2+3x+1$
3.d)	?	25140446	Hs	B/R	x^6+x^5+1	$x^6+3x^5+2x^3+1$

Table 1. Polynomial-based DNA sequences generated by BCH codes over Galois ring and field extensions. Abbreviations: TS targeting sequence; PM protein motifs; L labelings A, B, C and D; R ring; F field; *signal or transit peptide without experimental evidence. Sc *Saccharomyces cerevisiae*; Ts *Triticum aestivum*; Nt *Nicotiana tabacum*; Cs *Citrus sinensis*; At *Arabidopsis thaliana*; Hs *Homo sapiens*; Ib *Ipomoea batatas*; Pd *Polistes dominulus*; Mm *Mesobuthus martensii*.

instead provide evidence that this algorithm may be describing ancient site specific sequences in which evolution acted to influence the current appearance of the gene. This was also observed in the wPR4 gene, which is involved in vacuolar defense in *Triticum aestivum*, in which the residue alterations in the positions suggested by the algorithm were found in eudicots, monocots, and other more distant taxa. The code-generated nucleotide sequence of the hevein-like protein PR4 of *Arabidopsis thaliana* showed an alteration that was also found in eudicots and monocots. Based on these results, one may infer the possibility that the ECC generated sequence might represent a plesiomorphic state of the SNP on DNA sequences of interest, and, may be viewed as an alternative generator of the canonical genetic code.

This SNP plesiomorphic state evidence is supported by a Bayesian analysis and divergence time calculation for the code-generated and homologous sequences of the *Arabidopsis thaliana* malate dehydrogenase gene. The analyses showed that the *A. thaliana* malate dehydrogenase sequences form a monophyletic group rooted in the sequence generated by the ECC (Fig. 1). This sequence was generated by the Klein-linear code ((1023, 1013, 3) BCH code over Z_4 with the generator polynomial $g(x) = x^{10} + x^9 + x^8 + 3x^7 + x^6 + x^4 + x^3 + 3x + 1$ and labeling C, Tables 2 and 3) and was recovered as an external group for *A. thaliana* clade (Fig. 1). The divergence time analysis indicates that the MDH code-generated sequence node has diverged approximately 1 MYA before the development of any *A. thaliana* paralogous sequences. These observations suggest that the sequence generated by the code might be more closely related to the ancestor of *A. thaliana* malate dehydrogenase rather than to other paralogous genes, evidencing that the ECC code generated sequence has a SNP that may be indicating the ancient state of this sequence. The application of an ECC does not aim to reconstruct full ancestral sequences from a given phylogenetic tree and aligned gene sequences of some current species; here we describe an ancestral site specific reconstruction based solely on DNA primary structure recovered from coding and decoding gene sequences.

Among the analyzed sequences, we identified several single nucleotide polymorphisms that were pointed out by the ECC as leading to a codon alteration (and also an amino acid alteration in the translated sequence), but in the deviant genetic codes, these altered codons correspond to the same amino acids that were found in the original sequence^{15,26,27}.

In noncanonical genetic codes, alterations in the components of the translation mechanism confer different meanings to specific codons. For example, TGA is read as Trp^{17,27–38}, AGA as Ser^{33–37}, ATA as Met^{17,31,35,37–40}, and TGA as Cys^{17,23}.

When the F1 ATPase gene from *Ipomoea batatas* (GI 217937) was applied to the DNA Sequence Generator Algorithm, the output sequence presented an alteration in the sense codon TGG (encoding Trp) to become the stop codon TGA (Table 4a). A similar example is observed in the BRCA1 gene sequence in *H. sapiens* (GI 25140446), which is altered by the code from Cys to a stop codon (Table 4b). Interestingly, in the mitochondrial genetic code of most organisms, aside from green plants, the codon TGA is associated with tryptophan, and studies have shown that in the primary structure of

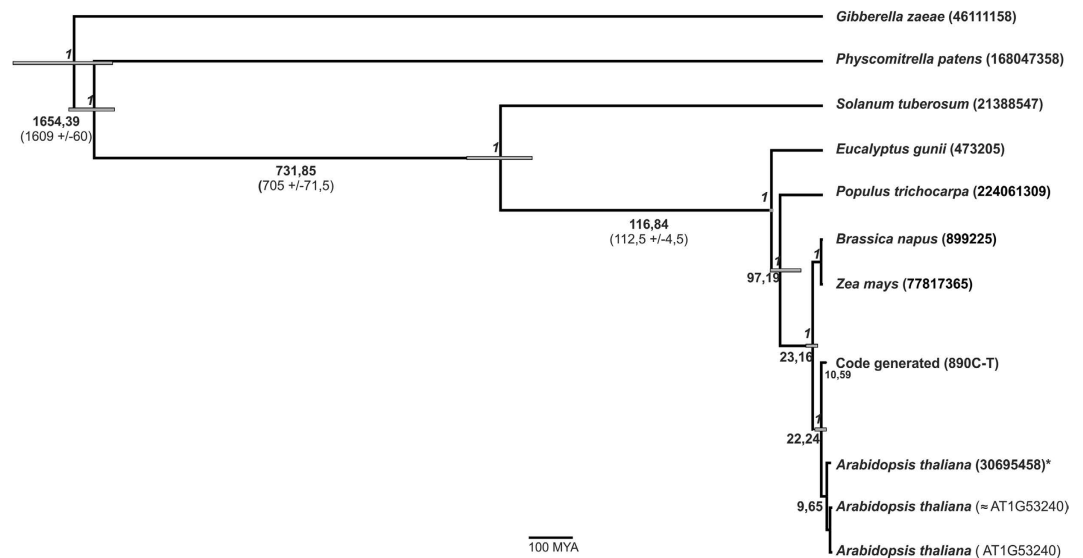


Figure 1. The malate dehydrogenase (MDH) phylogenetic proposal and date inference used to estimate the divergence time among malate dehydrogenase (MDH) sequences. The number on the nodes indicates the posterior probability, and the number along the length of the branch indicates the age in millions of years ago (MYA). The asterisk indicates the sequence analyzed by the G-linear code.

mitochondrial and nuclear genomes, the TGA codon does not signal for the release of the transcription factors but instead codes for Trp^{17,28,30,38}.

The code generated sequence for the Allergen Pol d5 gene of *Polistes dominulus* (GI 51093376) showed an alteration from AGT (Ser) to AGA (Arg), the same happening with the code generated sequence for the anti-epilepsy peptide precursor of *Mesobuthus martensii* (GI 16740522) showed an alteration from ATG (Met) to ATA (Ile) (Table 4b,c). In noncanonical genetic codes, AGA codes for Ser^{33–37} and ATA for Met^{17,35,37,39–41}; therefore, these alterations could modify the folding and activity of the subsequent protein due to a change in the charge and hydrophobicity of the residues.

Often times, the same codon reassignment may independently occur multiple times in different taxa. The mechanisms leading to codon reassignment have yet to be fully elucidated and may be due to factors such as codon disappearance, an ambiguous intermediate, or unassigned codons^{16,17,42–44}. Deviant genetic codes are an example of how populations cross over maladaptive valleys from one adaptive peak to another, in respect to error minimization, via adaptive bridges⁴⁵. Therefore, the algorithm may underlie any of the stages of information transmission, representing an earlier stage of the evolution of the universal/canonical code.

The characters, character states, and the evolution of ancient genes or proteins can hardly be directly studied, because such molecule are rarely preserved over the evolutionary time or from any ancestral, living or preserved, has not been gathered from the nature. Pauling and Zuckerkandl once proposed that ancestral molecules could one day be “resurrected” by digging out from the evolution their ancient form⁴⁶. Since then, different methods of ancestral sequence reconstruction (ASR) have emerged based on parsimony⁴⁷, Bayesian inference⁴⁸ or maximum likelihood⁴⁹. Independently of the methodology used all these approaches rely on multiple sequence alignment with the aim of elucidating the complete and distant sequences (Supplementary material 1 presents a maximum likelihood analysis for the *Arabidopsis thaliana* Malate Dehydrogenase). Here, we hypothesize that the G-linear code may identify the original molecular primary structure of the sequence using only the intrinsic nucleotide composition. The DNA sequence generation algorithm can describe the plesiomorphic state of certain DNA character state sequences, as the suggested single nucleotide alteration often occurs in distant taxa and is maintained by alternative codon patterns in noncanonical genetic codes.

In summary, the G-linear code, commonly associated with reliable digital transmission, even with all the constraints inherent to the construction of the ECC^{4–7}, unwraps the molecular component of every living cell when it is applied to the primary structure of DNA, thus revealing ancient information that may have been silenced by assorted evolutionary pressures that have shaped the present forms of life. This code generates point mutations that can be found in actual (real) sequences, and the DNA sequence generation algorithm can be used in computer simulations for the analysis of polymorphisms and mutations.

Klein-linear code((1023,1013,3) Primitive BCH code over $GR(4,10)$)

Coding strand: $p(x) = x^{10} + x^9 + x^8 + x^7 + x^6 + x^4 + x^3 + x + 1$ - $g(x) = x^{10} + x^9 + x^8 + 3x^7 + x^6 + x^4 + x^3 + 3x + 1$

Labeling C: (0,2,1,3) - (A,C,G,T)

Oaa:	M	F	R	S	M	L	V	R	S	S	A	S	A	K	Q	A	V	I	R	R	S
Ont:	ATG	TTC	AGA	TCT	ATG	CTC	GTC	CGA	TCT	TCT	GCC	TCC	GCG	AAG	CAG	GCG	GTT	ATC	CGC	CGT	AGC
Olb:	031	332	010	323	031	232	132	210	323	323	122	322	121	001	201	121	133	032	212	213	012
Glb:	031	332	010	323	031	232	132	210	323	323	122	322	121	001	201	121	133	032	212	213	012
Gnt:	ATG	TTC	AGA	TCT	ATG	CTC	GTC	CGA	TCT	TCT	GCC	TCC	GCG	AAG	CAG	GCG	GTT	ATC	CGC	CGT	AGC
Gaa:	M	F	R	S	M	L	V	R	S	S	A	S	A	K	Q	A	V	I	R	R	S
Oaa:	F	S	S	G	S	V	P	E	R	K	V	A	I	L	G	A	A	G	G	I	G
Ont:	TTC	TCC	TCC	GGC	TCC	GTC	CCC	GAG	CGT	AAA	GTC	GCC	ATC	CTT	GGT	GCC	GCC	GGT	GGA	ATT	GGT
Olb:	332	322	322	112	322	132	222	101	213	000	132	122	032	233	113	122	122	113	110	033	113
Glb:	332	322	322	112	322	132	222	101	213	000	132	122	032	233	113	122	122	113	110	033	113
Gnt:	TTC	TCC	TCC	GGC	TCC	GTC	CCC	GAG	CGT	AAA	GTC	GCC	ATC	CTT	GGT	GCC	GCC	GGT	GGA	ATT	GGT
Gaa:	F	S	S	G	S	V	P	E	R	K	V	A	I	L	G	A	A	G	G	I	G
Oaa:	Q	P	L	A	L	L	M	K	L	N	P	L	V	S	S	L	S	L	Y	D	I
Ont:	CAG	CCT	CTT	GCT	CTC	CTC	ATG	AAG	CTT	AAT	CCT	CTT	GTC	TCT	TCC	CTC	TCC	CTC	TAC	GAT	ATC
Olb:	201	223	233	123	232	232	031	001	233	003	223	233	132	323	322	232	322	232	302	103	032
Glb:	201	223	233	123	232	232	031	001	233	003	223	233	132	323	322	232	322	232	302	103	032
Gnt:	CAG	CCT	CTT	GCT	CTC	CTC	ATG	AAG	CTT	AAT	CCT	CTT	GTC	TCT	TCC	CTC	TCC	CTC	TAC	GAT	ATC
Gaa:	Q	P	L	A	L	L	M	K	L	N	P	L	V	S	S	L	S	L	Y	D	I
Oaa:	A	N	T	P	G	V	A	A	D	V	G	H	I	N	T	R	S	E	V	V	G
Ont:	GCT	AAC	ACT	CCT	GGA	GTT	GCT	GAT	GTT	GGT	CAC	ATC	AAC	ACC	AGA	TCT	GAG	GTT	GTT	GGA	
Olb:	123	002	023	223	110	133	123	123	103	133	113	202	032	002	022	010	323	101	133	133	110
Glb:	123	002	023	223	110	133	123	123	103	133	113	202	032	002	022	010	323	101	133	133	110
Gnt:	GCT	AAC	ACT	CCT	GGA	GTT	GCT	GAT	GTT	GGT	CAC	ATC	AAC	ACC	AGA	TCT	GAG	GTT	GTT	GGA	
Gaa:	A	N	T	P	G	V	A	A	D	V	G	H	I	N	T	R	S	E	V	V	G
Oaa:	Y	M	G	D	D	N	L	A	K	A	L	E	G	A	D	L	V	I	I	P	A
Ont:	TAC	ATG	GGC	GAT	GAT	AAC	TTG	GCC	AAA	GCT	CTT	GAA	GGA	GCT	GAT	CTC	GTT	ATC	ATT	CCA	GCT
Olb:	302	031	112	103	103	002	331	122	000	123	233	100	110	123	103	232	133	032	033	220	123
Glb:	302	031	112	103	103	002	331	122	000	123	233	100	110	123	103	232	133	032	033	220	123
Gnt:	TAC	ATG	GGC	GAT	GAT	AAC	TTG	GCC	AAA	GCT	CTT	GAA	GGA	GCT	GAT	CTC	GTT	ATC	ATT	CCA	GCT
Gaa:	Y	M	G	D	D	N	L	A	K	A	L	E	G	A	D	L	V	I	I	P	A
Oaa:	G	V	P	R	K	P	G	M	T	R	D	D	L	F	N	I	N	A	G	I	V
Ont:	GGT	GTA	CCA	AGG	AAG	CCT	GGT	ATG	ACC	CGT	GAC	GAT	CTT	TTC	AAC	ATT	AAT	GCT	GGA	ATT	GTC
Olb:	113	130	220	011	001	223	113	031	022	213	102	103	233	332	002	033	003	123	110	033	132
Glb:	113	130	220	011	001	223	113	031	022	213	102	103	233	332	002	033	003	123	110	033	132
Gnt:	GGT	GTA	CCA	AGG	AAG	CCT	GGT	ATG	ACC	CGT	GAC	GAT	CTT	TTC	AAC	ATT	AAT	GCT	GGA	ATT	GTC
Gaa:	G	V	P	R	K	P	G	M	T	R	D	D	L	F	N	I	N	A	G	I	V
Oaa:	K	N	L	C	T	A	I	A	K	Y	C	P	H	A	L	I	N	M	I	S	N
Ont:	AAG	AAC	CTT	TGC	ACT	GCC	ATC	GCC	AAG	TAC	TGC	CCA	CAT	GCG	CTT	ATT	AAT	ATG	ATC	AGC	AAC
Olb:	001	002	233	312	023	122	032	122	001	302	312	220	203	121	233	033	003	031	032	012	002
Glb:	001	002	233	312	023	122	032	122	001	302	312	220	203	121	233	033	003	031	032	012	002
Gnt:	AAG	AAC	CTT	TGC	ACT	GCC	ATC	GCC	AAG	TAC	TGC	CCA	CAT	GCG	CTT	ATT	AAT	ATG	ATC	AGC	AAC
Gaa:	K	N	L	C	T	A	I	A	K	Y	C	P	H	A	L	I	N	M	I	S	N
Oaa:	P	V	N	S	T	V	P	I	A	A	E	I	F	K	K	A	G	M	Y	D	E
Ont:	CCT	GTG	AAC	TCT	ACT	GTT	CCA	ATT	GCA	GCT	GAG	ATA	TTT	AAG	AAG	GCT	GGT	ATG	TAC	GAT	GAA
Olb:	223	131	002	323	023	133	220	033	120	123	101	030	333	001	001	123	113	031	302	103	100
Glb:	223	131	002	323	023	133	220	033	120	123	101	030	333	001	001	123	113	031	302	103	100
Gnt:	CCT	GTG	AAC	TCT	ACT	GTT	CCA	ATT	GCA	GCT	GAG	ATA	TTT	AAG	AAG	GCT	GGT	ATG	TAC	GAT	GAA
Gaa:	P	V	N	S	T	V	P	I	A	A	E	I	F	K	K	A	G	M	Y	D	E
Oaa:	K	K	L	F	G	V	T	T	L	D	V	V	R	A	R	T	F	Y	A	G	K
Ont:	AAG	AAA	TTG	TTT	GGT	GTT	ACC	ACT	CTT	GAC	GTC	GTC	AGG	GCC	AGG	ACT	TTC	TAT	GCT	GGA	AAG
Olb:	001	000	331	333	113	133	022	023	233	102	132	132	011	122	011	023	332	303	123	110	001
Glb:	001	000	331	333	113	133	022	023	233	102	132	132	011	122	011	023	332	303	123	110	001
Gnt:	AAG	AAA	TTG	TTT	GGT	GTT	ACC	ACT	CTT	GAC	GTC	GTC	AGG	GCC	AGG	ACT	TTC	TAT	GCT	GGA	AAG
Gaa:	K	K	L	F	G	V	T	T	L	D	V	V	R	A	R	T	F	Y	A	G	K

Table 2. *A. thaliana* - Mitochondrial - Malate dehydrogenase 1 – GI number 30695458.

Methods

Identification of the DNA sequences. Although several DNA-encoding sequences (organelle-targeting sequences, introns, protein motifs, and full proteins) were identified by the corresponding G-linear codes over finite Galois rings and fields, as shown in Table 1, the majority of these DNA sequences were identified by the G-linear codes over rings. One possible explanation is that the latter algebraic structure may be more flexible than the algebraic structure of fields. As a consequence, the sequences identified by the corresponding G-linear codes over fields exhibit less adaptability than those offered by G-linear codes over rings. This observation suggests that it is possible to classify the proteins according to their

Oaa:	A	N	V	P	V	A	E	V	N	V	P	V	I	G	G	H	A	G	V	T	I
Ont:	GCA	AAT	GTC	CCA	GTT	GCA	GAA	GTT	AAT	GTT	CCG	GTG	ATT	GGT	GGT	CAT	GCT	GGG	GTT	ACT	ATT
Olb:	120	003	132	220	133	120	100	133	003	133	221	131	033	113	113	203	123	111	133	023	033
Glb:	120	003	132	220	133	120	100	133	003	133	221	131	033	113	113	203	123	111	133	023	033
Gnt:	GCA	AAT	GTC	CCA	GTT	GCA	GAA	GTT	AAT	GTT	CCG	GTG	ATT	GGT	GGT	CAT	GCT	GGG	GTT	ACT	ATT
Gaa:	A	N	V	P	V	A	E	V	N	V	P	V	I	G	G	H	A	G	V	T	I
Oaa:	L	P	L	F	S	Q	A	T	P	Q	A	N	L	S	S	D	I	L	T	A	L
Ont:	CTC	CCT	CTC	TTC	TCT	CAG	GCA	ACT	CCT	CAA	GCC	AAC	TTG	TCA	AGT	GAC	ATA	CTT	ACC	GCC	CTT
Olb:	232	223	232	332	323	201	120	023	223	200	122	002	331	320	013	102	030	233	022	122	233
Glb:	232	223	232	332	323	201	120	023	223	200	122	002	331	320	013	102	030	233	022	122	233
Gnt:	CTC	CCT	CTC	TTC	TCT	CAG	GCA	ACT	CCT	CAA	GCC	AAC	TTG	TCA	AGT	GAC	ATA	CTT	ACC	GCC	CTT
Gaa:	L	P	L	F	S	Q	A	T	P	Q	A	N	L	S	S	D	I	L	T	A	L
Oaa:	T	K	R	T	Q	D	G	G	T	E	V	V	E	A	K	A	G	K	G	S	A
Ont:	ACT	AAG	CGT	ACC	CAA	GAT	GGA	GGT	ACA	GAA	GTC	GTG	GAG	GCA	AAA	GCA	GGA	AAA	GGT	TCA	GCT
Olb:	023	001	213	022	200	103	110	113	020	100	132	131	101	120	000	120	110	000	113	320	123
Glb:	023	001	213	022	200	103	110	113	020	100	132	131	101	120	000	120	110	000	113	320	123
Gnt:	ACT	AAG	CGT	ACC	CAA	GAT	GGA	GGT	ACA	GAA	GTC	GTG	GAG	GCA	AAA	GCA	GGA	AAA	GGT	TCA	GCT
Gaa:	T	K	R	T	Q	D	G	G	T	E	V	V	E	A	K	A	G	K	G	S	A
Oaa:	T	L	S	M	A	Y	A	G	A	L	F	A	D	A	C	L	K	G	L	N	G
Ont:	ACA	TTG	TCC	ATG	GCC	TAT	GCC	GGA	GCA	TTG	TTC	GCT	GAT	GCA	TGC	TTG	AAA	GGA	CTC	AAC	GGT
Olb:	020	331	322	031	122	303	122	110	120	331	332	123	103	120	312	331	000	110	232	002	113
Glb:	020	331	322	031	122	303	122	110	120	331	332	123	103	120	312	331	000	110	232	002	113
Gnt:	ACA	TTG	TCC	ATG	GCC	TAT	GCC	GGA	GCA	TTG	TTC	GCT	GAT	GCA	TGC	TTG	AAA	GGA	CTC	AAC	GGT
Gaa:	T	L	S	M	A	Y	A	G	A	L	F	A	D	A	C	L	K	G	L	N	G
Oaa:	V	P	D	V	I	E	C	S	Y	V	Q	S	T	I	T	E	L	P	F	F	A
Ont:	GTT	CCA	GAT	GTC	ATA	GAA	TGC	TCA	TAC	GTG	CAA	TCT	ACA	ATC	ACC	GAG	CTT	CCT	TTC	TTT	GCC
Olb:	133	220	103	132	030	100	312	320	302	131	200	323	020	032	022	101	233	223	332	333	122
Glb:	133	220	103	132	030	100	312	320	302	131	200	323	020	032	022	101	333	223	332	333	122
Gnt:	GTT	CCA	GAT	GTC	ATA	GAA	TGC	TCA	TAC	GTG	CAA	TCT	ACA	ATC	ACC	GAG	TTT	CCT	TTC	TTT	GCC
Gaa:	V	P	D	V	I	E	C	S	Y	V	Q	S	T	I	T	E	F	P	F	F	A
Oaa:	S	K	V	R	L	G	K	N	G	V	E	E	V	L	D	L	G	P	L	S	D
Ont:	TCG	AAG	GTG	AGG	TTG	GGG	AAG	AAT	GGT	GTG	GAG	GAG	GTT	CTT	GAC	TTG	GGA	CCA	CTC	TCA	GAC
Olb:	321	001	131	011	331	111	001	003	113	131	101	101	133	233	102	331	110	220	232	320	102
Glb:	321	001	131	011	331	111	001	003	113	131	101	101	133	233	102	331	110	220	232	320	102
Gnt:	TCG	AAG	GTG	AGG	TTG	GGG	AAG	AAT	GGT	GTG	GAG	GAG	GTT	CTT	GAC	TTG	GGA	CCA	CTC	TCA	GAC
Gaa:	S	K	V	R	L	G	K	N	G	V	E	E	V	L	D	L	G	P	L	S	D
Oaa:	F	E	K	E	G	L	E	A	L	K	P	E	L	K	S	S	I	E	K	G	V
Ont:	TTT	GAG	AAG	GAA	GGC	TTG	GAA	GCA	TTG	AAG	CCA	GAA	CTC	AAG	TCC	TCC	ATA	GAA	AAG	GGA	GTC
Olb:	333	101	001	100	112	331	100	120	331	001	220	100	232	001	322	322	030	100	001	110	132
Glb:	333	101	001	100	112	331	100	120	331	001	220	100	232	001	322	322	030	100	001	110	132
Gnt:	TTT	GAG	AAG	GAA	GGC	TTG	GAA	GCA	TTG	AAG	CCA	GAA	CTC	AAG	TCC	TCC	ATA	GAA	AAG	GGA	GTC
Gaa:	F	E	K	E	G	L	E	A	L	K	P	E	L	K	S	S	I	E	K	G	V
Oaa:	K	F	A	N	Q																
Ont:	AAG	TTT	GCC	AAC	CAG																
Olb:	001	333	122	002	201																
Glb:	001	333	122	002	201																
Gnt:	AAG	TTT	GCC	AAC	CAG																
Gaa:	K	F	A	N	Q																

Table 3. *A. thaliana* - Mitochondrial - Malate dehydrogenase 1 - GI number 30695458. Abbreviations: Oaa = original amino acid, Ont = original nucleotide, Olb = original labeling; Glb: generated labeling; Gnt: generated nucleotide; Gaa: generated amino acid. Red: shows where the error occurred in the targeting sequences. $p(x)$ = primitive polynomial; $p(x)'$ = reciprocal polynomial of $p(x)$. $g(x)$ = generator polynomial; $g(x)'$ = reciprocal generator polynomial of $g(x)$.

stability in the mutation index, allowing a new approach for the classification of DNA sequences from a mathematical point of view.

All of the DNA sequences analyzed by the DNA sequence generation algorithm were identified as belonging to the “cloud” of the corresponding code words of the ECC. In other words, the actual DNA sequences differ from the corresponding code words of the ECC by a single nucleotide. The code-generated sequences in which the single nucleotide alteration led to an amino acid change in the translated protein were further analyzed.

These code-generated sequences were used as queries in a Blastx search, with the results filtered for green plants, fungi, bacteria, Archaea, algae and monocots from the NCBI non-redundant protein sequence database. The Blastx results were then aligned with Muscle^{50,51} (CLC Bio Genomics workbench plugin) and the position of the altered amino acid was compared with these results.

Several codons with the same meaning have been reassigned in independent lineages, which could mean that there is an underlying predisposition towards certain reassignments⁴³. As an example of how

a) *I. batatas* – Mitochondrial – F1ATPase delta subunit – GI number 217937

G-linear code ((63,57,3) Primitive BCH code over GF(64), labeling D: (A=0,C=1,G=a,T=b))

Coding strand: $p(x) = x^3 + ax^2 + ax + a$ - $g(x) = x^6 + x^5 + x^3 + x^2 + 1$

Oaa: M F R H S S R L L A R A T T M G W R R P F
 Ont: ATG TTC AGG CAC TCT TCT CGA CTC CTA GCT CGC GCC ACC ACA ATG GGG TGG CGT CGC CCC TTC
 Olb: 0ba bb1 0aa 101 b1b b1b 1a0 1b1 1b0 a1b 1a1 a11 011 010 0ba aaa ba0 1ab 1a1 111 bb1
 Glb: 0ba bb1 0aa 101 b1b b1b 1a0 1b1 1b0 a1b 1a1 a11 011 010 0ba aaa ba0 1ab 1a1 111 bb1
 Gnt: ATG TTC AGG CAC TCT TCT CGA CTC CTA GCT CGC GCC ACC ACA ATG GGG TGA CGT CGC CCC TTC
 Gaa: M F R H S S R L L A R A T T M G sto R R P F

b) *P. dominulus* – Endoplasmic reticulum – Allergen Pol d 5 – GI number 51093376

G-linear code ((63,57,3) Primitive BCH code over GF(64), labeling D: (A=0,C=1,G=a,T=b))

Coding strand: $p(x) = x^3 + ax^2 + bx + b$ - $g(x) = x^6 + x^5 + 1$

Oaa: M K I S C L I C L V I V L T I I H L S Q A
 Ont: ATG AAA ATT AGT TGC TTA ATT TGT CTC GTA ATT GTT CTT ACG ATC ATT CAT TTG TGT CAA GCT
 Olb: 0ba 000 0bb 0ab ba1 bb0 0bb bab 1b1 ab0 0bb abb 1bb 01a 0b1 0bb 10b bba b1b 100 a1b
 Glb: 0ba 000 0bb 0a0 ba1 bb0 0bb bab 1b1 ab0 0bb abb 1bb 01a 0b1 0bb 10b bba b1b 100 a1b
 Gnt: ATG AAA ATT AGA TGC TTA ATT TGT CTC GTA ATT GTT CTT ACG ATC ATT CAT TTG TGT CAA GCT
 Gaa: M K I R C L I C L V I V L T I I H L S Q A

c) *M. martensii* – Endoplasmic reticulum – anti-epilepsy peptide precursor – GI number 16740522

Z₄-linear code ((63,57,3) Primitive BCH code over GR(4,6), labeling A: (A=0,C=1,G=3,T=2))

Coding strand: $p(x) = x^6 + x^5 + x^4 + x + 1$ - $g(x) = x^6 + x^5 + x^4 + 2x^2 + 3x + 1$

Oaa: M K L F L L L V I S A S M L I D G L V N A
 Ont: ATG AAA CTA TTT CTT TTA CTA GTT ATC TCT GCT TCA ATG CTA ATT GAT GGC TTA GTT AAT GCT
 Olb: 023 000 120 222 122 220 120 322 021 212 312 210 023 120 022 302 331 220 322 002 312
 Glb: 023 000 120 222 122 220 120 322 021 212 312 210 020 120 022 302 331 220 322 002 312
 Gnt: ATG AAA CTA TTT CTT TTA CTA GTT ATC TCT GCT TCA ATA CTA ATT GAT GGC TTA GTT AAT GCT
 Gaa: M K L F L L L V I S A S I L I D G L V N A

d) *H. sapiens* – truncated breast and ovarian cancer susceptibility protein (BRCA1) gene, exon 12 and partial cds - GI number 25140446

Z_{2x2}-linear code ((63,57,3) Primitive BCH code over GR(4,6), labeling B: (A=0,C=1,G=2,T=3))

Coding strand: $p(x) = x^6 + x^5 + 1$ - $g(x) = x^6 + 3x^5 + 2x^3 + 1$

Oaa: E A A S G C E S E T S V S E D C S G L S E
 Ont: GAA GCA GCA TCT GGG TGT GAG AGT GAA ACA AGC GTC TCT GAA GAC TGC TCA GGG CTA TCA GAG
 Olb: 200 210 210 313 222 323 202 023 200 010 021 231 313 200 201 321 310 222 130 310 202
 Glb: 200 210 210 313 222 320 202 023 200 010 021 231 313 200 201 321 310 222 130 310 202
 Gnt: GAA GCA GCA TCT GGG TGA GAG AGT GAA ACA AGC GTC TCT GAA GAC TGC TCA GGG CTA TCA GAG
 Gaa: E A A S G sto E S E T S V S E D C S G L S E

Table 4. DNA sequences generated by BCH code. Abbreviations: Oaa = original amino acid, Ont = original nucleotide, Olb = original labeling; Glb: generated labeling; Gnt: generated nucleotide; Gaa: generated amino acid. Red: shows where the alteration has occurred in the targeting sequences. $p(x)$ = primitive polynomial ; $p(x)'$ = reciprocal polynomial of $p(x)$. $g(x)$ = generator polynomial ; $g(x)'$ = reciprocal generator polynomial of $g(x)$.

the DNA sequence generation algorithm could be determining the ancient codon patterns in the analyzed species, we searched for codons in the code-generated sequences that were related to meaningful biological parts of nuclear or mitochondrial genomes^{16,27} and had a codon reassignment in other species.

Evolutionary proposal and estimation of the divergence time based on Bayes approach - Estimates of divergence time among malate dehydrogenase (MDH) sequences. The divergence time between fungi and green plants⁵², mosses and vascular plants^{52,53} and eudicot rosids and asterids⁵⁴ was used to estimate a divergence time for the *Arabidopsis thaliana* group. Species-level phylogenies were generated using a Bayesian uncorrelated lognormal relaxed clock model in Beast version 1.4.8⁵⁵. The dataset followed the GTR + Γ model of substitution implemented in Beast, and two Monte Carlo Markov chains were run for 90,000,000 generations, using the Yule speciation model, using a 10% burn-in with sampling trees generated every 10,000 generations.

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Author Contributions

M.M.B. conducted all of the phylogenetic and computational biology analyses. L.S. performed the codon reassignment search and analyses. L.C.B.F., A.S.L.R. and R.P.J. developed the DNA-SGA, L.C.B.F. and A.S.L.R. assembled the code-generated sequence database. M.M.B., M.C.S.F. and R.P.J. proposed the main concept of this manuscript, and M.C.S.F. and R.P.J. jointly supervised the work. L.S., L.C.B.F. and A.S.L.R. contributed equally to the work.

Additional Information

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