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CRISPR technology challenge facing the numerical integrity of whole human genome DNA

Abstract

Background: Global analysis of 3 human genomes of increasing levels of evolution (Neanderthal/Sapiens Build34/Sapiens hg38) reveals 2 levels of numerical constraints controlling, structuring and optimizing these genome's DNA sequences. A global constraint - called "HGO" for "Human Genome Optimum"-optimizes the genome at its global scale. The same operator applied to each of the 24 individual chromosomes reveals a hierarchical structure of these 24 chromosomes.

Results: Then analysing the single strand DNA CG/TA proportions at whole chromosomes and genome scale reveals strong fine-tuned numerical ratios evidencing the "closure" nature (Varela's autopoiesis theory) of whole human genome.

Keywords: human genome, CRISPR,; biomathematics, evolution autopoiesis, DNA

Volume 1 Issue 6 - 2017

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Received: July 27, 2017 | **Published:** October 05, 2017

Introduction

Thanks to the CRISPR (Clustered regularly interspaced short palindromic repeats) technology, it is now possible to locally modify the genomes, and particularly the human genome.[1] Almost simultaneously, the fractal and global structures of the human genome were demonstrated.[2] In such a context, apart from ethical questions, can a local technology as powerful as CRISPR be applied, ignoring its possible effect on the possible global and long-range equilibria and balancing at the chromosome scale or even the entire genome scale? For more than 25 years, we have been looking for possible global, even numerical, structures that would organize DNA, genes, chromosomes and even whole genomes.[3–9] We have already demonstrated a numerical structure at the scale of each human chromosome as well as on the whole genome.[10–15] In[10] we have already highlighted this numerical value of 0.6909830056, the HGO (Human Genome Optimum) in this article: it controls the population of triplets codons analysing single stranded DNA sequence from the whole human genome.

Materials and methods

Analysed whole human genomes

We analyzed completely and systematically each of the 24 chromosomes of each of the following three reference genomes:

Neanderthal genome: (2014) ref[16]

http://www.nature.com/nature/journal/v505/n7481/full/nature12886.html

Sapiens Build34 (2003) human reference genome ref[17]

http://www.nature.com/nature/journal/v431/n7011/full/nature03001.html

Sapiens hg38 (2013) human reference genome ref[18]

https://www.ncbi.nlm.nih.gov/grc/human

Computing the HGO (Human Genome Optimum): let us now distinguish the two types of HGO that will be discussed

1/Theoretical HGO (tHGO)

tHGO=(3-Phi)÷2=0.6909830056, where Phi is the Golden Ratio Phi=1.618033989

2/Reference female HGO (rwHGO): rwHGO=0.6913477936

Error (tHGO – rwHGO) = 0.6909830056 - 0.6913477936 = ¯0.0003647879784

and

Reference male HGO (rmHGO): rmHGO=0.6922864236

Error (tHGO – rmHGO) = 0.6909830056 - 0.6922864236 = ¯0.001303417973

Details: HGOwoman=[(sum C+G single strand 1 to 22 chromosomes)+(sum C+G chrX)+(sum C+G single strand 1 to 22 chromosomes)+(sum C+G chrX)]/[(sum T+A single strand 1 to 22 chromosomes)+(sum T+A chrX)+(sum T+A single strand 1 to 22 chromosomes)+(sum T+A chrX)]

HGOman=[(sum C+G single strand 1 to 22 chromosomes)+(sum C+G chrX)+(sum C+G single strand 1 to 22 chromosomes)+(sum C+G chrY)]/[(sum T+A single strand 1 to 22 chromosomes)+(sum T+A chrX) + (sum T+A single strand 1 to 22 chromosomes)+(sum T+A chrY)]

Results and discussion

In all that follows, the general methodology will be as follows: we calculate, for the 46 chromosomes constituting each genome studied, only the single-stranded DNA sequences. In these sequences, we count the relative populations of bases T+A on the one hand, and C+G on the other hand.

I/ Genome unity

HGO of the 3 whole genomes: Neanderthal, Sapiens Build34 and Sapiens HG38: The three genomes we compare here are differentiated on the one hand by their respective evolution levels, on the other hand by the sample of individual genomes of which they form the syntheses, and finally by the precision of the sequencing of DNA.

The detailed analysis related to the 3 whole genomes shows the various distances and errors between real computed HGOs for

each genome and theoretical HGO optimum value=0.6909830055. Particularly, it is found that the 3 HGOs calculated for the respective 3 genomes of Neanderthal, Sapiens (2003 Build34 and 2013 hg38 Sapiens) are very close to the ideal theoretical optimal HGO=0.6909830056 (99.67% for the least optimal genome). It is also observed that female genomes (XX) are more optimal than male genomes (XY). On the other hand, the genomes of Neanderthal and Sapiens (Build34 of 2003) have very close optimization levels. We believe these results from the fact that the precisions of their respective DNA sequencing are similar. On the contrary, the hg38 genomes of 2013 show the most optimal levels, this is most certainly due to the deeper quality of their DNA sequencing. Figure 1 summarises HGO results for these 3 human genomes of varying levels of evolution.

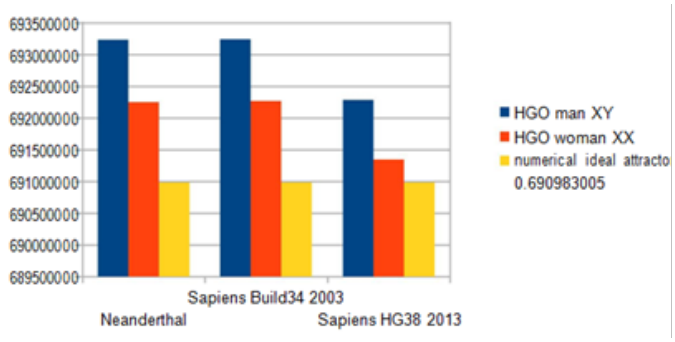

Figure 1 The respective HGOs of 3 human genomes of varying levels of evolution are shown here.

Considerations on this theoretical Human Genetic Optimum (HGO) of (3–Phi)/2

This formula is particularly simple. We can even make it more "beautiful", indeed:

Since 1+Phi=Phi*2, we can write:

(3–Phi)/2=C+G/T+A=(4–(1+Phi))/2=(4–(Phi*2))/2=(2*2–Phi*2)/2=C+G/T+A

This new equivalent formula contains only the numbers "2" and "Phi".

This omnipresence of the number "2" in this formula has a strong analogy with the predictive formula of the periodic table of the Mendeleiev elements, also built around the "2".[19]

A second track to be studied could consist in replacing this writing by:

(3–Phi)/2=(3–Phi)/(5-3)=C+G/T+A

By this artifice of writing, we thus make the "3" appear in the numerator and the denominator (!)

The formula then becomes:

(3-Phi)x(T+A)=2x(C+G)=(5-3) x (C+G)

3(T+A)+3(C+G)=5(C+G)+Phi(T+A)

3(T+A+C+G)=5(C+G)+Phi(T+A)

Therefore, if we consider that the single copy (single strand DNA) of the 24 chromosomes whole genomes XX or XY all lead to the same attractor HGO=(3-Phi)/2, to write:

Considering the cumulative population of 24 chromosomes of the single human genome (single strand DNA)

We check the following perfect balance: "THREE times the whole genome (T+A+C+G)=FIVE times (C+G) PLUS Phi times (T+A)"

Verification on 24 hg38 chromosomes single strand DNA:

CG=1200551672

TA=1737087441

3×(CG+TA)=8812917339

(5×CG)+(PHI×TA)=8813424881

8812917339÷881342488=0.9999424126

8812917339-881342488=¯507542

Finally, it is remarkable that this formula is based on integers 3 or 5. In fact, these numbers are very small integers and they are Fibonacci numbers. It will therefore be interesting to postpone the error calculations on the accuracy of these two integers 3 and 5:

(5×CG)+(Phi×TA)=8813424881/(CG+TA)=2937639113

8813424881/2937639113=3.000172772

and

3×(CG+TA)=8812917339

-

(Phi×TA)=2810666521

8812917339 -2810666521=6002250818

CG=1200551672

6002250818÷CG=4.999577243

The exact formula can then be written:

3.000172772(T+A+C+G)=5(C+G)+Phi(T+A)

or

3(T+A+C+G)=4.999577243 (C+G)+Phi(T+A)

2/Chromosomes hierarchy

HGO spectral hierarchy of the 24 human chromosomes

The following 2 figures (Figure 2) and (Figure 3) illustrate the hierarchical spectrum of the individual HGOs of each of the 24 chromosomes for each of the three genomes analyzed. It should be noted that the upstream/ downstream tipping point lies between chromosomes 14 and 21, which is closely related to the probable mechanisms explaining trisomy21 (whose disorders involve precisely these two chromosomes). Finally, we note that it is the downstream region (Figure 3) that contributes the most to the superiority of optimality of sapiens hg38 compared to sapiens Build34. We have sorted the 24 chromosomes by increasing values of CG/TA ratios in the 3 cases of compared genomes. It then reveals a hierarchical classification scale of 24 chromosomes ranging from 1/Phi (chromosome4) to 3/2 Phi (chromosome 19).

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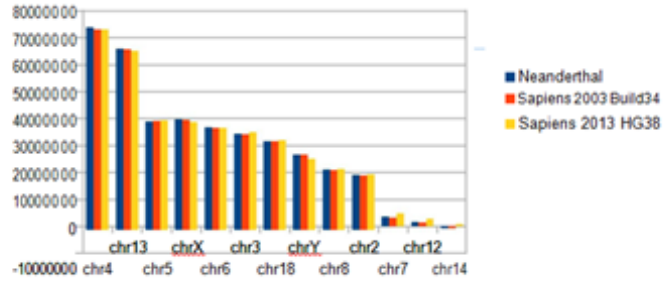

Figure 2 « UP » chromosomes: HGO diversity of human chromosomes UPSTREAM of the numerical attractor.

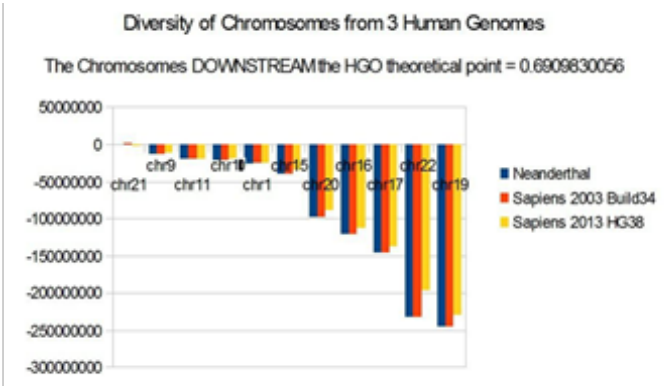

Figure 3 « Down » chromosomes: Diversity of HGOs of human chromosomes DOWNSTREAM of the numerical attractor HGO=0.6909830056.

3/Cohesion chromosomes/genome

About the hierarchical classification of 24 single stranded chromosomes

In the following, we demonstrate a real interaction, a kind of "dialogue" with feddback between the equilibrium of the whole genome and the part of each of the individual chromosomes. We must now regulate this high level of remarkable numerical constraints which seem to "frame" the CG and TA populations of each of the 24 human chromosomes on one hand and of the entire genome on the other hand. This will be verified for the human HG38 reference genome, but - as illustrated in Table 2 below - these remarkable properties will be extended to other higher primates in.[20] First, is there a simple relationship between HGO (P2), the numerical constraint at the scale of the entire genome, and the two extreme extremes of chromosome 4 (P1) and chromosome 19 (P3)? Then:

P1=1÷PHI=0.6180339887

P3=3 ÷ (2×PHI)=0.927050983

P2=(3-PHI)÷2=0.6909830055

We could compute:

P2-P1=0.07294901685

P3-P2=0.2360679775

Then, (P3-P2)÷(P2-P1)=3.236067979

Given that 2×PHI=3.236067978

Then, (P3-P2)÷(P2-P1)=2×PHI=3.236067979

In other hand, P3-P1=1÷(2×PHI)=0.3090169943

Then finally, the high level of strong numerical constraints applied simultaneously to the 2 extrema chromosomes and to the whole human genome:

P1: chr4 1/Phi

==>P2-P1=0.07294901685

P2: genome (3-Phi)/2

==> P3-P2=0.2360679775

P3: chr19 3/2 Phi

Then:

(P3-P2)÷(P2-P1) 3.236067979=2×PHI=3.236067978

P3-P1 0.3090169943 1÷(2×PHI) 0.3090169943

4/Closure

We will now demonstrate a very strong property of the human genome very close to the theory of the autopoiesis of my friend franco-chilian biologist Francisco Varela.[21,22] In this theory, the coherence, consistency and integrity of living systems are modeled: the DNA of the human genome is a wonderful illustration of this. Let us now look at the two UP chromosome populations (chr4 to chr14) and DOWN (chr21 to chr19). Would there exist particular constraints or remarkable relations on these 2 populations of chromosomes which determine the law described here? Let us recall in (Table 1) the respective populations and ratios of each of the 24 chromosomes of the genome HG38:

Then cumulating in Table1 he populations C+G and T+A in each subclass UP and DOWN:

UP=742398303 1124171661

DOWN=458153369 612915780

DOWN/UP: C+G T+A

0.6171260995 0.5452154695

or UP / DOWN : C+G T+A

1.62041437 1.834137246

This result is remarkable since it means that: on the one hand, the CG/TA ratio of chromosome4, a sort of leader or "semaphore", is equal to 1/Phi. On the other hand, the ratio of the C+G ratios between the 11 DOWN chromosomes to the 13 UP chromosomes is also equal to 1/Phi.

Table 1 Evidence of strong numerical constraints surrounding the relative populations C+G / T+A constituting the hierarchical meta structure of the 24 chromosomes in humans and large primates

Genome	Extremum top CG/TA chr4		Extremum down CG/TA chr19		Spectral limits (CG/TA chr19)-(CG/TA chr4)	
	value	Error CG/TA Chr4 vs 1/Phi	value	Error CG/TA chr19 vs 3/2 Phi	value	Error (3/2 Phi) – Spectral Limits
Sapiens HG38	0.619261918	¯0.0012279291	0.920811	0.006240148	0.301549	0.007468078

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Table Continued....

Genome	Extremum top CG/TA chr4		Extremum down CG/TA chr19		Spectral limits (CG/TA chr19)-(CG/TA chr4)	
	value	Error CG/TA Chr4 vs 1/Phi	value	Error CG/TA chr19 vs 3/2 Phi	value	Error (3/2 Phi) – Spectral Limits
Sapiens BUILD34	0.619377817	-0.001343828	0.936495	-0.009444177	0.317117	-0.00810035
neanderthal	0.618590097	-0.000556108	0.936648	-0.009596744	0.318058	-0.009040636
chimp	0.615238866	0.002795123	0.92794	-0.000888599	0.312701	-0.003683723
Orangutang	0.614364584	0.003669404	0.925221	0.001829533	0.310857	-0.001839871
gorilla	0.617745603	0.000288386	0.929942	-0.002890887	0.312196	-0.003179272
macaque	0.653660819	-0.035626831	0.929994	-0.002942726	0.276333	0.032684105

Table 2 Respective populations and ratios of each of the 24 chromosomes of human genome HG38 (2013)

Chromosome	C + G	T + A	(C + G)/(T + A)
Chromosomes UPSTREAM HGO point = (3-Phi) ÷ 2=0.6909830056			
4	72568001	117184666	0.619261918
13	37772797	60210328	0.627347471
5	71611274	109654104	0.653065151
X	61221521	93671508	0.653576763
6	67360020	102718502	0.655772998
3	78577742	119522393	0.657431131
18	31856106	48233499	0.660456045
Y	10572683	15842360	0.66736793
8	58133960	86634176	0.671028025
2	96769083	143779145	0.673039772
7	64696843	94273288	0.686269084
12	54275482	78862334	0.688230734
14	36982791	53585358	0.690165978
Chromosomes DOWNSTREAM HGO point = (3-Phi)÷2=0.6909830056			
21	16411625	23676994	0.693146478
9	50270473	71520077	0.70288617
11	55885058	78648684	0.71056571
10	55359481	77903481	0.710616269
1	96166571	134314441	0.715980875
15	35578844	49062481	0.725174171
20	28010605	35933652	0.779508996
16	36472718	45333225	0.804547173
17	37575444	45344760	0.828661217
22	18406838	20752939	0.886950904
19	28015712	30425046	0.920810835

Closure varela's theory

Distance amplitudes. CG/TA Down/Up=(P3-P2)/(P2-P1)=2 Phi

Distance populations CG Down/Up=CG Down/CG Up =1/Phi

Then, distance amplitudes Up/Down CG/TA=1/2Phi

Populations CG Down/CG Up=2 times Distance amplitudes CG/TA Up/Down.

It is remarkable to obtain this relation between AMPLITUDES on the one hand, and POPULATIONS (C + G) on the other hand. We thus find again this number "2", symbol of the doubling of frequency such as the octave shift in music ... suggesting the possible wave nature of the DNA.[23] We still have a lot to discover on this fascinating CODE that is DNA.[24–32]

Conclusion

In order to convince the most skeptical about this NUMERICAL UNIT of the human genome, it seemed judicious to use the analogy: By taking the notation invented by the mathematician Leibnitz, we will imagine a population of 3.5 billion "monads", basic TCAG nucleotides, constituting the single strand of DNA of our genome. In the course of human evolution, these Monads self-organized themselves into 23 clusters, the pairs of chromosomes. A first source of astonishment will be the finely adjusted "classification" of the 24 chromosomes: Indeed, the ratios of their respective populations (C+G)/(T+A) are not arbitrary, they adjust according to a kind of "Musical range" between 1/Phi (P1: chromosome 4) and 3/2 Phi (P3: chromosome 19). Let an amplitude of variation (P3-P1) equal to ½ Phi. Now this ratio 2 corresponds in the world of waves to a doubling of frequency while in the musical universe it corresponds to an octave. In addition, attenuation (here between P1 and P3) or variation factors of 1.5 (50%) are commonly used in acoustics, electronics and more generally in the physical sciences. A second source of astonishing will be this kind of "center of gravity", a kind of "average" constituted by this general ratio at the scale of the whole genome: P2:(C+G)/(T+A)=(3-Phi)/2=(4–(Phi*2))/2=(2*2–Phi*2)/2. The reader will notice both the simplicity and the "beauty" of this formula constructed around the number "2" (2 * 2 - Phi * 2)/2.

However, a third source of astonishment will come from the link, the numerical relationship uniting the 2 levels of organizations above: AUTONOMOUS organizations and DIVERSITY of each of the 24 chromosomes on the one hand and global organization and UNITY of the whole genome in other hand. How can one be surprised at this real COHESION between the diversified and perfectly "bounded" hierarchy of the 24 chromosomes and the unity of the entire genome? In fact, if (P3-P2) represents the chromosomes beyond the equilibrium point of the genome (3-Phi)/2 while (P2-P1) represents the chromosomes before the equilibrium point of the genome, then (P3-P2)/(P2-P1)=2 × Phi, whereas P3-P1=1/(2 × Phi). Again this famous "2" report uniting the cluster scales of individual chromosomes and

the entire genome scale. Finally, a fourth and last source of astonishing will be this evidence of a "closure" in the sense of the autopoiesis theory of Francisco Varela and Humberto Maturana: While, as a kind of "guide" chromosome, the chromosome4 "resonates" in a ratio (C+G)/(T+A)=1/Phi, on the one hand, the same "mirror resonance" in echo is discovered between the ratio of the populations (C+G) of the chromosomes "down" located after the genomic equilibrium point, and the population (C+G) of the set of « up » chromosomes before the genomic equilibrium point, here also 1/Phi. We can indeed speak of global cohesion of the genome because of this double constraint on the boundaries of the extreme chromosomes (P1: chr4 and P3: chr19) on the one hand, and on the contents of the C+G ratios of all other chromosomes Intermediaries on the other.

We can only conclude this "cohesion", this consistency of the human genome in the sense of the closing in a "feedback" or "closure" demonstrating that the human genome behaves like an "ALL", in harmony with each of its 24 chromosomes. Finally, our approach may be related to these hundreds of unpredictable mutations resulting from manipulation of genomes by CRISPR revolutionary technology.[33–35] Effectively in their 2017 article, authors note that « …/...They found that the technique had successfully corrected a gene that causes blindness in the mice, but the two mice that had undergone CRISPR gene-editing had sustained more than 1,500 unintended single-nucleotide mutations, and more than 100 larger deletions and insertions.

Acknowledgements

We especially thank Dr. Robert Friedman (MD. practiced nutritional and preventive medicine in Santa Fe, New Mexico), worlwide expert on Golden ratio applications. We also thank the mathematician Pr. Diego Lucio Rapoport (Buenos aires), the french biologist Pr. François Gros (Pasteur institute,co-discoverer of RNA messenger with James Watson and Walter Gilbert) and Pr. Luc Montagnier, medicine Nobel prizewinner for their interest in my research of biomathematical laws of genomes.

Conflict of interest

The author declares no conflict of interest.

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Citation: Perez JC. CRISPR technology challenge facing the numerical integrity of whole human genome DNA. *MOJ Biol Med.* 2017;1(6):167–172. DOI: 10.15406/mojbm.2017.01.00037