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Information Entropy of DNA Sequences for Survival Analysis

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Abstract: The purpose of this study is to provide an accurate formula for calculating entropy for short DNA sequences and to demonstrate how to use it to examine leukemia patient surviving. We used IDIBAPS leukemia patient's data base with 117 anonymized records. The generalized form of the Robust Entropy Estimator (*EnRE*) for short DNA sequences was proposed and key *EnRE* futures was showed. The Survival Analysis has been done using statistical package IBM SPSS. Entropy *EnRE* were calculated for leukemia patients for two samples: A. 2 groups divided by median *EnRE* and B. 2 groups of patients were formed according to their belonging to 1st and 4th quartiles of *EnRE*. The result of survival analysis are statistically significant: A. $p < 0.05$; B. $p < 0.005$. The death hazard for a patient with *EnRE* below median is 1.556 times that of a patient with *EnRE* over median and that the death hazard for a patient of 1st quartile (lowest *EnRE*) is 2.143 times that of a patient of 4th quartile (highest *EnRE*). The transition from median to quartile patients' groups with more *EnRE* differentiation confirmed the unique significance of the entropy of DNA sequences for leukemia patients surviving.

Keywords: information entropy; DNA sequences; patients surviving; leukemia

1. Introduction

Deoxyribonucleic acid (DNA) is not a random sequence of four nucleotides (A – adenine, C – cytosine, G – guanine, T – thymine) combinations: comprehensive reviews [1,2] persuasively shows long- and short-range correlations in DNA, periodic properties and correlations structure of sequences. Information theory methods imply quantifying the amount of information contained in sequences. According to a recent article in Cells [3], mammalian aging is greatly impacted by the reduction in quantity and quality of information in DNA sequences. Recognition of an organism's physiological age and backward rejuvenation of it are both highly dependent on the level of genetic and epigenetic information stored in DNA sequences. The information entropy by Claude Shannon was one of the first information measure for studied DNA sequences [4]. Nowadays, the Shannon's entropy implementations continue to be very successful for analyzing viral RNA, like SARC-COV-2 [5]. Thorough review of different entropy approaches 'to identify the formal connections between genetic diversity and the flow of information' was given in [6] and comprehensive review [7] puts state of art of information theory implementations for analyzing 'gene expression and transcriptomics, alignment-free sequence comparison, sequencing and error correction, genome-wide disease-gene association mapping, metabolic networks and metabolomics, and protein sequence, structure and interaction analysis'.

On the other hand, the relationship between entropy and patient survival is widespread in some branches of medicine and medical researches, as few examples:

1. ***Cardiology***: Used Approximated entropy based on Heart Rate Variability (HRV) for sudden cardiac death prognostication, evaluation of the effect of specific pharmacologic agents on HRV [8]; Used entropy based on Holter Electro-Cardiograms (ECG) and Heart Rate (HR) of normal

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cardiac dynamics and those with varying degrees of acute cardiac pathologies [9]; Consecutive post–myocardial infarction patients undergoing late gadolinium enhanced cardiac magnetic resonance (MR) with derived MR imaging tissue entropy. Patients were followed for appropriate implantable cardioverter-defibrillator therapy and mortality [10].

2. ***Neurology***: investigated the association of heart rate entropy (HRE) with mortality after intracerebral hemorrhage [11];
3. ***Surgery (general anesthesia)***: Entropy monitoring involves using electroencephalography (EEG) to assess the depth of general anesthesia in surgical patients [12] ;
4. ***Trauma***: For the categorisation of injury using entropies it is necessary to consider the underlying entropy of the individuals morbidity to which is added the entropy of trauma, which then may result in death [13]; Shown integer heart rate (HR) multiscale entropy (MSE), an indicator of complexity, predicts death based on long duration. Heart rate MSE within hours of admission predicts death occurring days later [14]; In this study measured both Shannon and Tsallis entropy of temperature signals in a cohort of critically ill patients. The reduced wavelet Shannon and Tsallis entropies of temperature signals may complement with sequential organ failure assessment in mortality prediction [15];
5. ***Oncology:*** used DNA copy number entropy (by array CGH DNA profile imaging) for survival analyzing of patients with esophageal adenocarcinoma [16]; used imaging texture analyzing entropy as predictive marker of promoter methylation status of the O^6-methylguanine-DNA methyltransferase in glioblastomas [17]; nuclear texture analysis measures the spatial arrangement of the pixel gray levels in a digitized microscopic nuclear image and is a promising quantitative tool for prognosis of cancer. It was evaluated the prognostic value of entropy-based adaptive nuclear texture features for patients with uterine sarcomas [18]; used nuclear texture analysis for detection of high-chromatin entropy nuclei. Chromatin entropy supplemented existing prognostic markers in multivariable analyses of three gynecological cancer cohorts [19].

Therefore, it appears there is a necessity for implementing advantages of information theory methods for exploration of relationship between mortality of some category of patients and entropy of their DNA sequences. The goal of this paper is to provide a reliable formula for calculating entropy accurately for short DNA sequences and to show how to use existing entropy analysis to examine the mortality of leukemia patients.

2. Materials and Methods

We used Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS) leukemia patient's data base (DB) with 117 anonymized records that consists: Date of patient's diagnosis, Date of patient's death, Leukemia diagnoses, Patient's DNA sequence. Average time for patient death after diagnoses: 99 ± 77 months. The formal characteristics of DNA sequences in UB leukemia patient's DB are: average number of bases N=496±69; min (N)=297 bases; max(N)=745 bases.

Statistically DNA is mostly close to uniform distribution but has exactly different non-uniform frequency patterns, e.g. base frequencies of *human mitochondrion* (16,569 bases) are A – 31%, C – 31%, G – 13%, T – 25% or *human fetal globin exons* (882 bases) are A – 24%, C – 25%, G – 28%, T – 22% [20]. We have shown comparison between real DNA sequence and simulated by uniform distribution on Figures 1 and 2:

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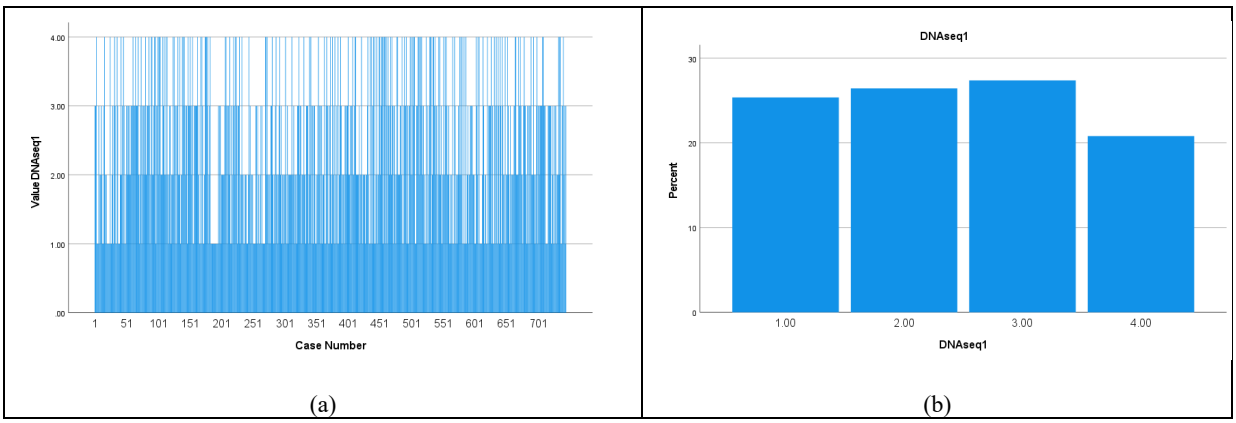

Figure 1. Real patient DNA sequence, N=745 bases (UB leukemia patient DB): (a) nucleotides distribution; (b) nucleotides frequenies (A – 1; C – 2; G – 3; T – 4).

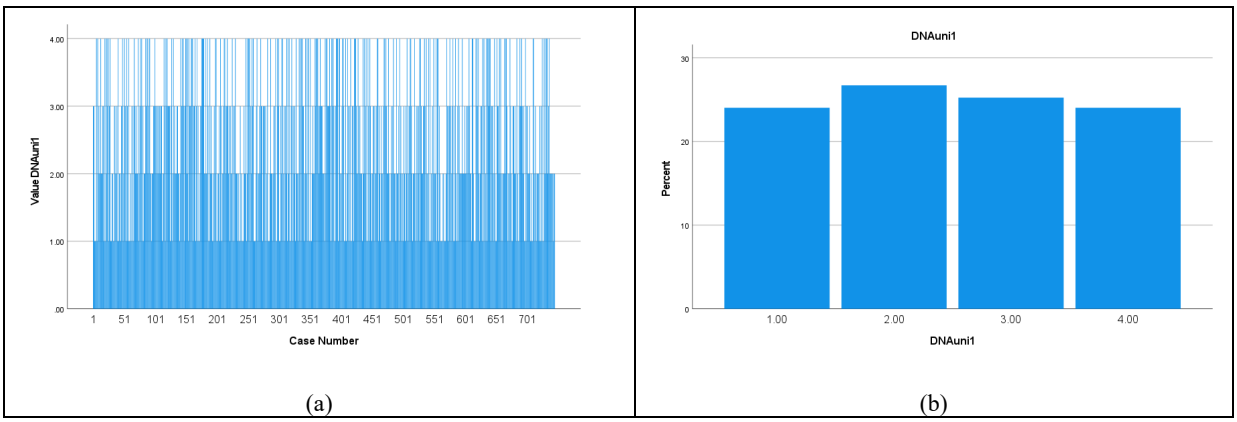

Figure 2. Simulated 4 elements sequence by Uniform distribution, N=745 bases:): (a) nucleotides distribution; (b) nucleotides frequenies (A – 1; C – 2; G – 3; T – 4).

Claude Shannon originally proposed the formula of information entropy in 1948 [21] and here is called Empirical Entropy (EnEmp) due to the limitations of time series:

$$EnEmp = -\sum_{i=1}^{N} P(x_i) ln(P(x_i)) \quad (1)$$

The problem of using the formula (1) in practice are:

- insensitivity to changing nucleotide positions in DNA sequence. There is sensitivity to changing of base only;
- low accuracy for small number of points in a time series (e.g. $N < 1000$);
- slow descending to an accurate value with the increasing length of sequence.

Shown in Table 2 is the dependency of accuracy of calculating entropy according to formula (1) on the length of a series for certain types of distribution of a random value. Accurate entropy values for associated distributions are given in Table 1.

Table 1. Various probability distributions and correspondent Entropy [22].

Distribution	**Probability density function**	**Entropy (*En*, nats)**
Normal Distribution	$f(x) = \frac{1}{\sigma\sqrt{2\pi}} exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$	$En = ln\left(\sqrt{2\pi\sigma^2}\right)$
Uniform Distribution	$f(x) = \frac{x}{b-a}$	$En = ln(b-a)$
Exponential Distribution	$f(x) = \lambda\, exp(-\lambda x)$	$En = 1 - ln(\lambda)$

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Lognormal Distribution	$f(x) = \frac{1}{x\sigma\sqrt{2\pi}} exp\left(-\frac{(ln(x)-\mu)^2}{2\sigma^2}\right)$	$En = \mu + ln\left(\sqrt{2\pi\sigma^2}\right)$
Pareto Distribution	$f(x) = \frac{\alpha x_m^{\alpha}}{x^{\alpha+1}}$	$En = ln\left(\frac{x_m}{\alpha}\right) + 1 + \frac{1}{\alpha}$

Table 2. Dependence from the length of time series of Entropy estimation accuracy and Correlation along simulated distribution parameters for various probability distributions.

Distribution	Length of sample	Empirical Entropy (*EnImp*)		Robust Entropy Estimator (*EnRE*)	
		Accuracy (Relative Error, %)	Correlation	Accuracy (Relative Error, %)	Correlation
Uniform Distribution (a = 0; b = 4)	N=100	6.92	0.978	4.71	0.991
	N =500	4.11	0.988	0.57	0.997
	N =1000	3.83	0.999	0.11	0.998
Normal Distribution (M = 1000; $\boldsymbol{\sigma = 100 - 200}$)	N=100	7.74	0.994	1.95	0.995
	N =500	1.83	0.997	0.35	0.998
	N =1000	0.91	0.999	0.16	0.999
Exponential Distribution ($\boldsymbol{\lambda = 0.0001 - 0.0011}$)	N=100	46.24	0.452	0.77	0.993
	N =500	28.38	0.903	0.25	0.997
	N =1000	19.31	0.950	0.06	0.999
Lognormal Distribution ($\boldsymbol{\mu = 7; \sigma = 0.002 - 0.012}$)	N=100	3.69	0.980	3.38	0.986
	N =500	1.17	0.997	0.49	0.997
	N =1000	0.80	0.999	0.22	0.999
Pareto Distribution ($\boldsymbol{\alpha}$ = 2; s = 1000 – 2000)	N=100	32.68	0.589	1.01	0.997
	N =500	17.78	0.867	0.35	0.998
	N =1000	14.75	0.946	0.12	0.999

The uniform distribution case (shown in Figures 1 and 2.) receives special attention, but other distributions are also taken into consideration as necessary examples of using numerical formulas for analysis of a limited series because it is not always possible to precisely match the observed DNA sequence with some fixed random distribution. We can acknowledge the impossibility of applying the formula (1) to a short times series $N < 1000$. Therefore, it would seem that developing a formula for accurately measuring entropy for a small number of DNA sequences is necessary.

Early in the last century, an Italian statistics professor Corrado Gini had proposed a way to measure the inequality among values of a frequency distribution (the Gini coefficient) [23]:

$$G = \frac{1}{2N^2M}\sum_{i=1}^{N}\sum_{j=1}^{N}\left(\left|x_i - x_j\right|\right), \qquad (2)$$

where M is a mean of x values. The Gini coefficient proved to be very popular in economics and sociology, and there are attempts to apply it to other areas as well, including HRV analyzing [24]. The Gini coefficient is an instance of generalized inequality index [25], and its alternative, as measure of deviation from balance — generalized entropy index — is derived from information theory as a measure of redundancy in data [26]. There are known limitations when using the Gini coefficient for data analysis: dependence on additive change of mean; a small selection substantially decreases the magnitude of the coefficient and etc.

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Therefore, following the analysis of known definitions of measures of deviation from balance and degree of order, a generalized form of the Robust Entropy Estimator (*EnRE*) for time series was proposed in [27] and adopted for DNA sequences now:

$$EnRE = ln\left(\frac{A}{N^{l/2}}\sum_{i=1}^{N}\sum_{j=1}^{N}\left(\frac{\left(|B_i - B_j||B_j - MD|\right)^{1/k}}{\left(D_{ij}\right)^{m/2}}\right)\right), \qquad (3)$$

where *MD* is median of the sequence for numerically coded bases *B*; D_{ij}- distance between B_i and B_j; *A, l, m, k* – estimated coefficients. Search conditions for coefficients *A, l, m, k* is the following:

1/accurate approximation for known distributions of a random value;

2/independence of *EnRE* from *N* for initial time series and for series after sorting;

3/independence of *EnRE* from additive changes of mean.

After numerical researches, final results of which are presented in Tab.2, the following coefficient values had been found: $l = 3$, $m = 1$, $k = 2$. Let us highlights some key futures of the discovered generalized form of *EnRE* and coefficients:

1/form of recording (3) and found coefficients *l, m, k* provide independence from additive change of mean series and from magnitude of selection *N* for basic series and for series after sorting;

2/value *EnRE* is sensitive to structural changes in series, such as, for example, sorting which increases the degree of order in series, decreasing the *EnRE*;

3/value *EnRE* is sensitive to change of nucleotide position in DNA sequence;

4/readjusting coefficient *A* alone may be required to find the best *EnRE* value in another range of change in parameters of various random distributions, which can always be done using the method of least squares.

The Survival Analysis has been done using statistical package IBM SPSS 27.

3. Results

3.1. Accuracy

First of all, let us test the accuracy of the proposed formula (3) for calculating entropy: Table 2 provides values of *EnRE* for various lengths of time series and various types of random distributions, and error values are given for each of these results when entropy is calculated and correlated with precise values when distribution parameters are changed. Let us note, that in all cases for $N = 500$, relative error in calculating the precise value of entropy does not exceed 1 %, while the magnitude of correlation is no worse than 0.995; in case of uniform and normal distribution the relative error for time series length N=500÷1000 are less than 0.6% and correlation is about 0.998.

3.2. Optimal DNA sequence coding

An initial DNA sequence's alphabet code should be converted into a numerical code of bases, but such permutation is arbitrary. We have used a principle of maximum entropy to avoid such arbitrariness. In Table 3, we present different numerical decoding of DNA sequences and their entropy values, standard deviations and coefficients of variation.

Table 3. Numerical decoding of DNA sequences and correspondent *EnRE*, standard deviation and coefficient of variation of *EnRE*.

Integer DNA code	Average Entropy *EnRE*	Standard deviation of *EnRE*	Coefficient of Variation (CV)
A=1,C=2,G=3,T=4 or A=4,C=3,G=2,T=1	1.205	0.030	0.025
A=2,C=1,G=3,T=4 or A=3,C=4,G=1,T=2	1.254	0.036	0.029

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A=3,C=4,G=2,T=1	1.241	0.034	0.027
A=1,C=4,G=3,T=2	1.235	0.043	0.035
A=1,C=3,G=4,T=2	1.221	0.040	0.033
A=1,C=3,G=2,T=4	1.211	0.033	0.027
A=1,C=2,G=4,T=3	1.223	0.039	0.032
A=-2, C=-1, G=1, T=2 (reflection symmetry by modulus)	1.430	0.023	0.016
A=-1, C=-2, G=1, T=2 (translation symmetry by modulus)	**1.470**	**0.022**	**0.015**

We can assume that, according to the *EnRE* properties, any symmetric change in integer decoding gives the same *EnRE* value (see the first two rows of Table 3); only one minimal and symmetric numerical decoding about zero gives the maximum for *EnRE* (bolded in Table 3). An additional, there is the minimal standard deviation and coefficient of variation for this numerical coding (A=-1, C=-2, G=1, T=2). Furthermore, this optimization rule reduced the self-influence of numerical decoding variance. A biochemical interpretation of this optimal coding is possible: A and G are purines that coded as -1 and +1; C and T are pyrimidines that coded as -2 and +2. The pairs A-T and G-C are complementary as purine to pyrimidine and "-" to "+". Thus, numerical decoding arbitrariness was removed by only one possible integer combination.

3.3. Leukemia patient's surviving

The entropy *EnRE* was calculated for all Leukemia patients after optimal integer decoding generated by a translation symmetry group (A = -1, C = -2, G = 1, T = 2).

3.3.1. Median groups

All patients were divided by median *EnRE* = 1.47 for 2 groups:

1. Group '1', 58 patients, *EnRE* below median;
2. Group '2', 59 patients, *EnRE* over median.

On Figure 3, we present the frequencies of DNA bases for both groups divided by median *EnRE*. There is no any significant changes in the frequencies of DNA bases between groups, thus statistical significance of difference in *EnRE* means is mainly caused by differences in the ordering of patients' DNA nucleotides in the groups.

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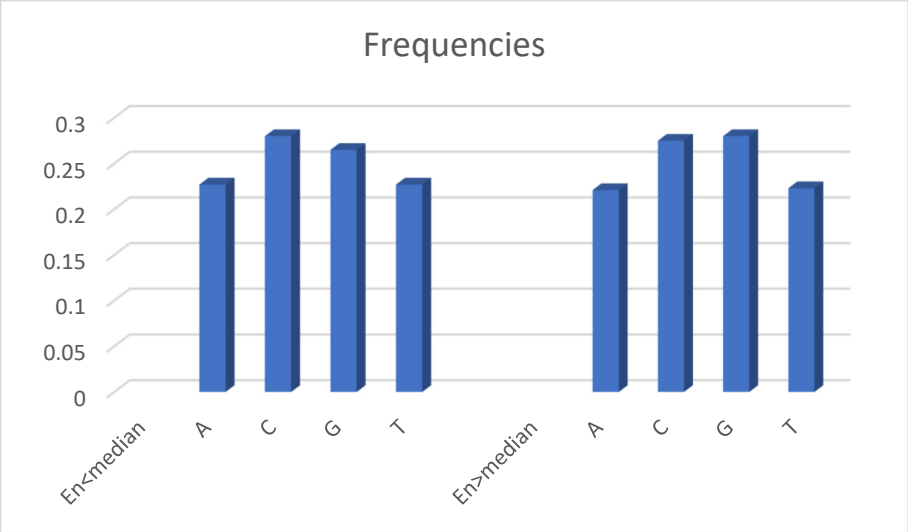
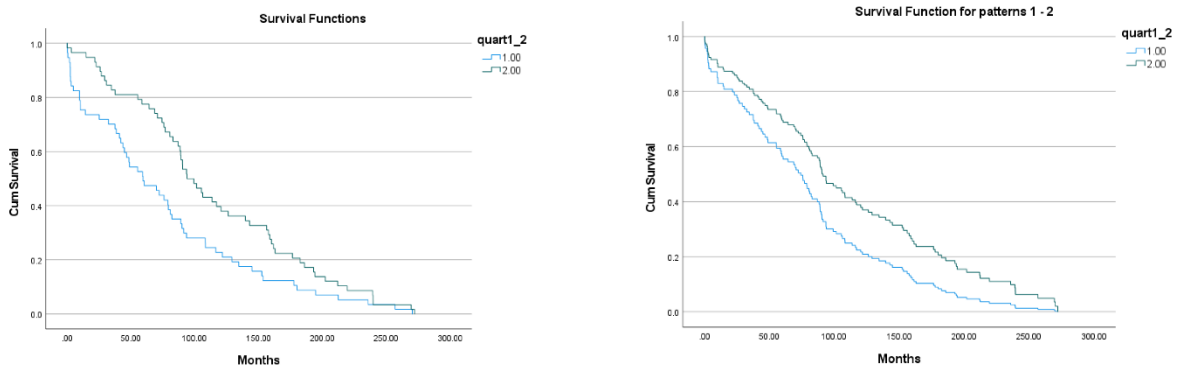


Figure 3. Frequencies of DNA bases for both groups divided by median *EnRE*.

The result of Kaplan-Meier survival analysis is given on Figure 4 (a). All overall comparisons show statistical significance: p=0.015 for Log Rank (Mantel-Cox); p=0.002 for Breslow (Generalized Wilcoxon); p=0.003 for Tarone-Ware. Descriptive statistics for all groups are given in final Table 5.



(a) **(b)**

Figure 4. Kaplan-Meier (**a**) and Cox Regressions survival plot (**b**) for median groups.

The result of Cox Regressions survival modelling is given on Figure 4 (b). All overall comparisons show statistical significance: p=0.015 for Omnibus test of model coefficients; p=0.016 for variables in equation with '-2 Log Likelihood'=862.2. The value of *Exp(B)* for model variable shows that the death hazard for a patient with *EnRE* below median is 1.556 times that of a patient with *EnRE* over median.

3.3.2. 1st and 4th quartiles groups

2 groups of patients were formed according to their belonging to 1st and 4th quartiles:

3. Group '1', 29 patients, *EnRE* ≤ 1.448, that is below 1st quartile;
4. Group '4', 29 patients, *EnRE* ≥ 1.490, that is over 4th quartile.

The result of Kaplan-Meier survival analysis is given on Figure 5 (a). All overall comparisons show statistical significance: p=0.005 for Log Rank (Mantel-Cox); p=0.003 for Breslow (Generalized Wilcoxon); p=0.003 for Tarone-Ware. Descriptive statistics for all groups are given in final Table 5.

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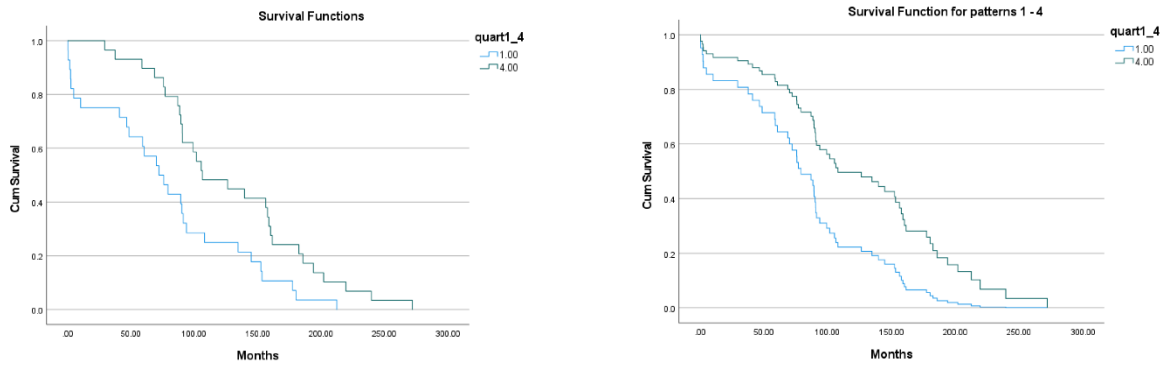

(a) **(b)**

Figure 5. Kaplan-Meier (**a**) and Cox Regressions survival plot (**b**) (1st and 4th quarterlies).

The result of Cox Regressions survival modelling is given on Figure 5 (b). All overall comparisons show statistical significance: p=0.005 for Omnibus test of model coefficients; p=0.005 for variables in equation with '-2 Log Likelihood'=345.4. The value of *Exp(B)* for model variable shows that the death hazard for a patient of 1st entropy quartile (lowest *EnRE*) is 2.143 times that of a patient of 4th entropy quartile (highest *EnRE*).

3.3.3. Immunoglobulin Variable Heavy Chain Gene (IgVH) mutated and unmutated subtypes

In article [28], it is shown: 'Chronic lymphocytic leukemia (CLL) presents two subtypes which have drastically different clinical outcomes, IgVH mutated (M-CLL) and IgVH unmutated (U-CLL)'. I was indicated that 'U-CLL, the more aggressive type of the disease, shows significantly increased variability of gene expression across patients and that, overall, genes that show higher variability in the aggressive subtype are related to cell cycle, development and inter-cellular communication.' It will be actual to establish a relation between leukemia patient surviving and entropy DNA sequences for IgVH subtypes M-CLL and U-CLL. For this purpose, we used the 177 leukemia patients' UB database, where M-CLL and U-CLL distributions between groups divided by entropy are shown in Table 4.

Table 4. Leukemia patient's entropy (*EnRE*) of DNA sequences groups and IgVH subtypes.

IgVH subtype	**Entropy of DNA sequences groups, number of patients**			
	Below median	**Over median**	**1st quartile**	**4th quartile**
Mutated (M-CLL)	26	16	13	9
Unmutated (U-CLL)	32	43	16	20

We did not find statisticaly significant differences of M-CLL and U-CLL *EnRE* neither for equality of means nor for equality of variance. The survival analysis shows statistical significance only for M-CLL stratum in both cases: median groups and 1st and 4th quartiles groups.

3.3.4. Combined analyzing for median entropy groups and M-CLL, U-CLL subtypes

We constructed a two-dimensional (2D) space for deeply analyzing of each factor influencing (*EnRE* and IgVH subtypes) on leukemia patients surviving. On the Figure 6 showed two leukemia patient's groups for surviving analysis:

1. *EnRE* below median (Low) and U-CLL;
2. *EnRE* over median (High) and M-CLL.

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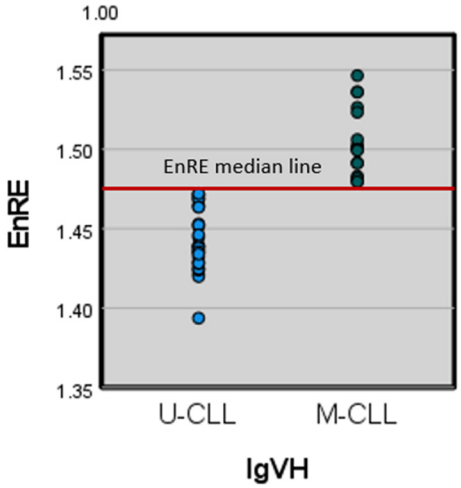
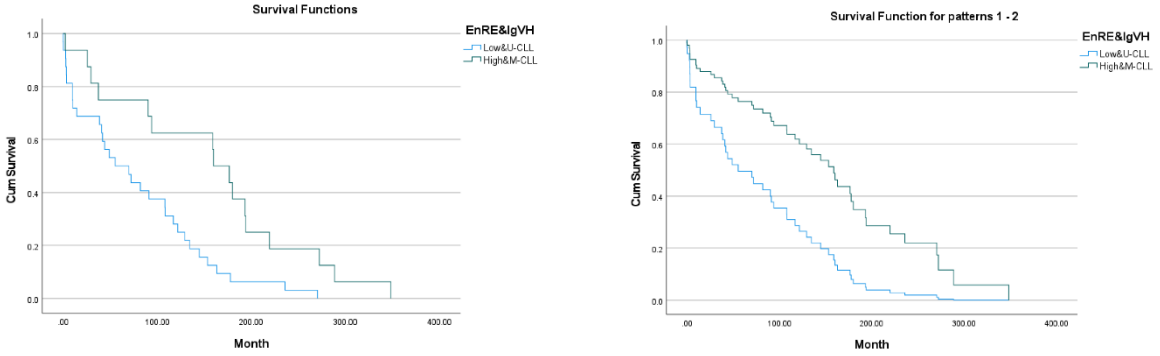


Figure 6. 2D leukemia patients separation by EnRE median and IgVH subtypes.

The result of Kaplan-Meier survival analysis is given on Figure 7 (a). All overall comparisons show statistical significance: p=0.004 for Log Rank (Mantel-Cox); p=0.014 for Breslow (Generalized Wilcoxon); p=0.007 for Tarone-Ware. Descriptive statistics for all groups are given in final Table 5.



(a) **(b)**

Figure 7. Kaplan-Meier (**a**) and Cox Regressions survival plot (**b**) (combined groups).

Table 5. Summary table for leukemia patient's surviving analysis.

Groups		Number of patients	Average *EnRE* ± SE	Average time of surviving ± SE , months	Hazard	Significance
Median	Below med. (Low)	58	1.442 ± 0.003	76.4 ± 9	1.56	$p < 0.05$
	Over med. (High)	59	1.504 ± 0.003	114.3 ± 9	1	
Quarter	1st quart. (Lowest)	29	1.425 ± 0.003	78.6 ± 11	2.14	$p < 0.005$
	4rd quart. (Highest)	29	1.519 ± 0.005	129.6 ± 11	1	
Median & IgVH subtypes	Low & U-CLL	32	1.443 ± 0.003	78.2 ± 13	2.61	$p < 0.01$
	High &	16	1.505 ± 0.005	154.3 ± 25	1	

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M-CLL

The result of Cox Regressions survival modelling is given on Figure 7 (b). All overall comparisons show statistical significance: p=0.005 for Omnibus test of model coefficients; p=0.004 for variables in equation with '-2 Log Likelihood'=272.8. The value of *Exp(B)* for model variable shows that the death hazard for a patient of Low&U-CLL is 2.611 times that of a patient of High&M-CLL.

The Generalized Linear Mixed Model (GLMM) can be performed for predictions of months from leukemia diagnosis to patient's death based on evaluation of entropy *EnRE* level and IgVH subtype. The model is statistically significant on the level of $p < 0.05$ for a whole model, intercept and each variable:

$$\text{Months} = 30.09*\text{IgVH} + 37.43 * \text{EnMed} + 69.65, \text{ months.} \quad (4)$$

Where, IgVH = 0 for U-CLL subtype, IgVH = 1 for M-CLL subtype; EnMed = 0 for *EnRE* below median and EnMed = 1 for *EnRE* over median. Thus, proposed GLMM suggests that the combination of a mutated IgVH subtype and a high entropy of DNA sequence over the median can double the minimal life expectancy of leukemia patients from diagnosis to death.

4. Discussion

The generalized form of Robust Entropy Estimator (3), which has been effectively used to calculate entropy values for a variety of random distributions (Tables 1 and 2), is proposed in this paper for DNA sequences of a finite length (N ≈500). We have formulated generalized parameters estimation rules for Entropy Robust Estimator (3). Important characteristics of the found generalized form of *EnRE* and coefficients are:

1/sensitive to change of nucleotide position in DNA sequence;

2/value *EnRE* is sensitive to structural changes in series, such as, for example, sorting which increases the degree of order in series, decreasing the *EnRE*;

3/form of recording (3) and found coefficients *l, m, k* provide independence from additive change of mean series and from magnitude of selection *N* for basic series and for series after sorting;

4/readjusting coefficient *A* alone may be required to find the best *EnRE* value in another range of change in parameters of various random distributions, which can always be done using the method of least squares.

Using the proposed generalized form for Entropy Robust Estimator (3) for UB leukemia patient's database, we analyzed DNA sequences entropy and IgVH subtypes of leukemia patient's surviving:

Patients groups comparison:

A. ***Groups divided by median.*** Both, Kaplan-Meier survival analysis and Cox Regressions survival modelling, showed the statistically significant results for $p < 0.05$. The value of *Exp(B)* for Cox Regressions *model variable* shows that the death hazard for a patient with *EnRE* below median is 1.556 times that of a patient with *EnRE* over median. The relation of average time of death after diagnoses is 1.496 times more for patients with *EnRE* over median in compare with patients with *EnRE* below median.

B. ***Patients groups formed of 1st and 4th quarterlies.*** Both, Kaplan-Meier survival analysis and Cox Regressions survival modelling, showed the statistically significant results for $p < 0.005$. The value of *Exp(B)* for *model variable* shows that the death hazard for a patient of 1st entropy quartile (lowest *EnRE*) is 2.143 times that of a patient of 4th entropy quartile (highest *EnRE*). The relation of average time of death after diagnoses is 1.649 times more for patients of 4th entropy quartile in compare with patients of 1st entropy quartile.

C. ***Combined groups: Low&U-CLL and High&M-CLL.*** Both, Kaplan-Meier survival analysis and Cox Regressions survival modelling, showed the statistically significant results for $p < 0.01$. The value of *Exp(B)* for Cox Regressions *model variable* shows that the death hazard for a patient with *EnRE* below median & U-CLL is 2.611 times that of a patient with *EnRE* over median & M-

CLL. The relation of average time of death after diagnoses is 1.973 times more for patients with *EnRE* over median & M-CLL in compare with patients with *EnRE* below median & U-CLL.

Thus, the transition from median to 1st and 4th quartiles patients' groups with more *EnRE* differentiation between groups confirmed the unique significance of the entropy of DNA sequences for leukemia patient's surviving. This significance is proved statistically by increasing hazard and decreasing of average time of death after diagnoses for leukemia patients with lower entropy of DNA sequences.

Stratification by IgVH shows that entropy of DNA sequences survival analysis is statistically significant for mutated subgroup (M-CLL). Accordingly, the presented entropy-based DNA sequences analyzing and the proposed in [27] IgVH mutated/unmutated immunoglobulin subtypes dividing methods complement each other and provide additional accuracy for mutated subgroup patients. A Generalized Linear Mixed Model suggests that the combination of a mutated IgVH subtype and a high entropy of DNA sequence over the median can double the minimal life expectancy of leukemia patients from diagnosis to death.

The future elaboration of current research is inclusion of more different patients' groups for exploration patient's surviving in relation with entropy DNA sequences as well as involving other methods of fractal analyses for DNA sequences, like fractal dimension or sequence reversibility.

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