

Google Matrix Analysis of DNA Sequences

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Abstract

For DNA sequences of various species we construct the Google matrix G of Markov transitions between nearby words composed of several letters. The statistical distribution of matrix elements of this matrix is shown to be described by a power law with the exponent being close to those of outgoing links in such scale-free networks as the World Wide Web (WWW). At the same time the sum of ingoing matrix elements is characterized by the exponent being significantly larger than those typical for WWW networks. This results in a slow algebraic decay of the PageRank probability determined by the distribution of ingoing elements. The spectrum of G is characterized by a large gap leading to a rapid relaxation process on the DNA sequence networks. We introduce the PageRank proximity correlator between different species which determines their statistical similarity from the view point of Markov chains. The properties of other eigenstates of the Google matrix are also discussed. Our results establish scale-free features of DNA sequence networks showing their similarities and distinctions with the WWW and linguistic networks.

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Introduction

The theory of Markov chains [1] finds impressive modern applications to information retrieval and ranking of directed networks including the World Wide Web (WWW) where the number of nodes is now counted by tens of billions. The PageRank algorithm (PRA) [2] uses the concept of the Google matrix G and allows to rank all WWW nodes in an efficient way. This algorithm is a fundamental element of the Google search engine used by a majority of Internet users. A detailed description of this method and basic properties of the Google matrix can be found e.g. in [3,4].

The Google matrix belongs to the class of Perron-Frobenius operators naturally appearing in dynamical systems (see e.g. [5]). Using the Ulam method [6] a discrete approximant of Perron-Frobenius operator can be constructed for simple dynamical maps following only one trajectory in a chaotic component [7] or using many independent trajectories counting their probability transitions between phase space cells [8,9], [10]. The studies of Google matrix of such directed Ulam networks provides an interesting and detailed analysis of dynamical properties of maps with a complex chaotic dynamics [7,8], [9,10].

In this work we use the Google matrix approach to study the statistical properties of DNA sequences of the species: *Homo sapiens* (HS, human), *Canis familiaris* (CF, dog), *Loxodonta africana* (LA, elephant), *Bos Taurus* (bull, BT), *Danio rerio* (DR, zebrafish), taken from the publicly available database [11]. The analysis of Poincaré recurrences in these DNA sequences [12] shows their similarities with the statistical properties of recurrences for dynamical trajectories in the Chirikov standard map and other symplectic maps [7]. Indeed, a DNA sequence can be viewed as a long symbolic trajectory and hence, the Google matrix, construct-

ed from it, highlights the statistical features of DNA from a new viewpoint.

An important step in the statistical analysis of DNA sequences was done in [13] applying methods of statistical linguistics and determining the frequency of various words composed of up to 7 letters. A first order Markovian models have been also proposed and briefly discussed in this work. Here we show that the Google matrix analysis provides a natural extension of this approach. Thus the PageRank eigenvector gives the frequency appearance of words of given length. The spectrum and eigenstates of G characterize the relaxation processes of different modes in the Markov process generated by a symbolic DNA sequence. We show that the comparison of word ranks of different species allows to identify proximity between species.

At present the investigations of statistical properties of DNA sequences are actively developed by various bioinformatic groups (see e.g. [14,15], [16], [17,18]). The development of various methods of statistical analysis of DNA sequences become now of great importance due to a rapid growth of collected genomic data. We hope that the Google matrix approach, which already demonstrated its efficiency for enormously large networks [2,3], will find useful applications for analysis of genomic data sets.

Results

Construction of Google matrix from DNA sequence

From [11] we collected DNA sequences of HS represented as a single string of length $L \approx 1.5 \cdot 10^{10}$ base pairs (bp) corresponding to 5 individuals. Similar data are obtained for BT ($2.9 \cdot 10^9$ bp), CF ($2.5 \cdot 10^9$ bp), LA ($3.1 \cdot 10^9$ bp), DR ($1.4 \cdot 10^9$ bp). For HS, CF, LA, DR the statistical properties of Poincaré recurrences in these

sequences are analyzed in [12]. All strings are composed of 4 letters A, G, C, T and undetermined letter N_l . The strings can be found at the web page [19].

For a given sequence we fix the words W_k of m letters length corresponding to the number of states $N = 4^m$. We consider that there is a transition from a state i to state j inside this basis N when we move along the string from left to right going from a word W_k to a next word W_{k+1} . This transition adds one unit in the transition matrix element $T_{ij} \rightarrow T_{ij} + 1$. The words with letter N_l are omitted, the transitions are counted only between nearby words not separated by words with N_l . There are approximately $N_l \approx L/m$ such transitions for the whole length L since the fraction of undetermined letters N_l is small. Thus we have $N_l = \sum_{i,j=1}^N T_{ij}$. The Markov matrix of transitions S_{ij} is obtained by normalizing matrix elements in such a way that their sum in each column is equal to unity: $S_{ij} = T_{ij} / \sum_i T_{ij}$. If there are columns with all zero elements (dangling nodes) then zeros of such columns are replaced by $1/N$. Such a procedure corresponds to one used for the construction of Google matrix of the WWW [2,3]. Then the Google matrix of DNA sequence is written as

$$G_{ij} = \alpha S_{ij} + (1 - \alpha) / N, \tag{1}$$

where α is the damping factor for which the Google search uses usually the value $\alpha \approx 0.85$ [3]. The matrix G belongs to the class of Perron-Frobenius operators. It has the largest eigenvalue $\lambda = \lambda_1 = 1$ with all other eigenvalues $|\lambda_i| \leq \alpha$. For WWW usually there are isolated subspaces so that at $\alpha = 1$ there are many degenerate $\lambda = 1$ eigenvalues [4] so that the damping factor allows to eliminate this degeneracy creating a gap between $\lambda = 1$ and all other eigenvalues. For our DNA Google matrices we find that there is already a significant spectral gap naturally present. In this case the PageRank vector is not sensitive to the damping factor being in the range $0.5 \leq \alpha \leq 1$ (other eigenvectors are independent of α [3,4], [9]). Due to that in the following we present all results at the value $\alpha = 1$.

The spectrum λ_i and right eigenstates $\psi_i(j)$ are determined by the equation

$$\sum_j G_{ji} \psi_i(j) = \lambda_i \psi_i(j). \tag{2}$$

The PageRank eigenvector $P(j)$ at $\lambda = 1$ has positive or zero elements which can be interpreted as a probability to find a random surfer on a given site j with the total probability normalized to unity $\sum_j P(j) = 1$. Thus, all sites can be ordered in a decreasing order of probability $P(j)$ that gives us the PageRank order index $K(j)$ with most frequent sites at low values of $K = 1, 2, \dots$

It is useful to consider the density of matrix elements $G_{KK'}$ in the PageRank indexes K, K' similar to the presentation used in [20,21] for networks of Wikipedia, UK universities, Linux Kernel and Twitter. The image of the DNA Google matrix of HS is shown in Fig. 1 for words of 5 and 6 letters. We see that almost all matrix is full that is drastically different from the WWW and other networks considered in [20] where the matrix G is very sparse. Thus the DNA Google matrix is more similar to the case of Twitter which is characterized by a strong connectivity of top PageRank nodes [21].

It is interesting to analyze the statistical properties of matrix elements G_{ij} . Their integrated distribution is shown in Fig. 2. Here N_g is the number of matrix elements of the matrix G with values $G_{ij} > g$. The data show that the number of nonzero matrix

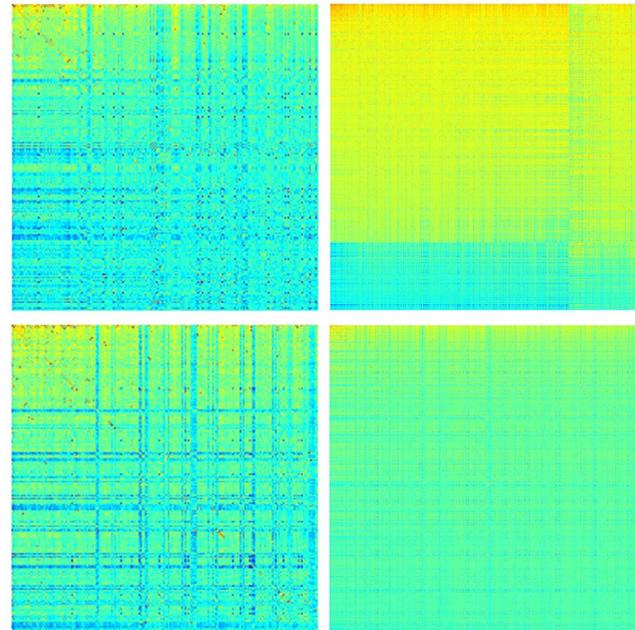


Figure 1. DNA Google matrix of Homo sapiens (HS) constructed for words of 5-letters (top) and 6-letters (bottom) length. Matrix elements $G_{KK'}$ are shown in the basis of PageRank index K (and K'). Here, x and y axes show K and K' within the range $1 \leq K, K' \leq 200$ (left) and $1 \leq K, K' \leq 1000$ (right). The element G_{11} at $K = K' = 1$ is placed at top left corner. Color marks the amplitude of matrix elements changing from blue for minimum zero value to red at maximum value. doi:10.1371/journal.pone.0061519.g001

elements G_{ij} is very close to N^2 . The main fraction of elements has values $G_{ij} \leq 1/N$ (some elements $G_{ij} < 1/N$ since for certain j there are many transitions to some node i' with $T_{i'j} \gg N$ and e.g. only one transition to other i'' with $T_{i''j} = 1$). At the same time there are also transition elements G_{ij} with large values whose fraction decays in an algebraic law $N_g \approx AN/g^{v-1}$ with some constant A and an exponent v . The fit of numerical data in the range $-5.5 < \log_{10} g < -0.5$ of algebraic decay gives for $m = 6$: $v = 2.46 \pm 0.025$ (BT), 2.57 ± 0.025 (CF), 2.67 ± 0.022 (LA), 2.48 ± 0.024 (HS), 2.22 ± 0.04 (DR). For HS case we find $v = 2.68 \pm 0.038$ at $m = 5$ and $v = 2.43 \pm 0.02$ at $m = 7$ with the average $A \approx 0.003$ for $m = 5, 6, 7$. There are visible oscillations in the algebraic decay of N_g with g but in global we see that on average all species are well described by a universal decay law with the exponent $v \approx 2.5$. For comparison we also show the distribution N_g for the WWW networks of University of Cambridge and Oxford in year 2006 (data from [4,20]). In these networks we have $N \approx 2 \cdot 10^5$ and on average 10 links per node. We see that in these cases the distribution N_g has a very short range in which the decay is at least approximately algebraic ($-5.5 < \log_{10}(N_g/N^2) < -6$). In contrast to that for the DNA sequences we have a large range of algebraic decay.

Since in each column we have the sum of all elements equal to unity we can say that the differential fraction $dN_g/dg \propto 1/g^v$ gives the distribution of outgoing matrix elements which is similar to the distribution of outgoing links extensively studied for the WWW networks [3,23], [24,25]. Indeed, for the WWW networks all links in a column are considered to have the same weight so that these matrix elements are given by an inverse number of outgoing links [3]. Usually the distribution of outgoing links follows a power law decay with an exponent $\tilde{v} \approx 2.7$ even if it is known that this

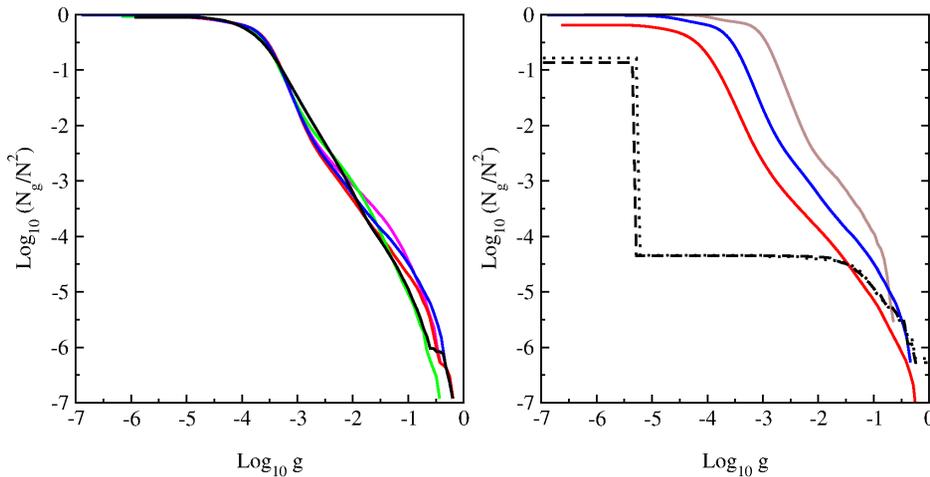


Figure 2. Integrated fraction N_g/N^2 of Google matrix elements with $G_{ij} > g$ as a function of g . *Left panel* : Various species with 6-letters word length: bull BT (magenta), dog CF (red), elephant LA (green), Homo sapiens HS (blue) and zebrafish DR(black). *Right panel* : Data for HS sequence with words of length $m = 5$ (brown), 6 (blue), 7 (red). For comparison black dashed and dotted curves show the same distribution for the WWW networks of Universities of Cambridge and Oxford in 2006 respectively. doi:10.1371/journal.pone.0061519.g002

exponent is much more fluctuating compared to the case of ingoing links. Thus we establish that the distribution of DNA matrix elements is similar to the distribution of outgoing links in the WWW networks with $\nu \approx \tilde{\nu}$. We note that for the distribution of outgoing links of Cambridge and Oxford networks the fit of numerical data gives the exponents $\tilde{\nu} = 2.80 \pm 0.06$ (Cambridge) and 2.51 ± 0.04 (Oxford).

It is known that on average the probability of PageRank vector is proportional to the number of ingoing links [3]. This relation is established for scale-free networks with an algebraic distribution of links when the average number of links per node is about 10 to 100 that is usually the case for WWW, Twitter and Wikipedia networks [4,20], [21,22], [23,24], [25]. Thus in such a case the matrix G is very sparse. For DNA we find an opposite situation where the Google matrix is almost full and zero matrix elements are practically absent. In such a case an analogue of number of ingoing links is the sum of ingoing matrix elements $g_s = \sum_{j=1}^N G_{ij}$. The integrated distribution of ingoing matrix elements with the dependence of N_s on g_s is shown in Fig. 3. Here N_s is defined as the number of nodes with the sum of ingoing matrix elements being larger than g_s . A significant part of this dependence, corresponding to large values of g_s and determining the PageRank probability decay, is well described by a power law $N_s \approx BN/g_s^{\mu-1}$. The fit of data at $m=6$ gives $\mu = 5.59 \pm 0.15$ (BT), 4.90 ± 0.08 (CF), 5.37 ± 0.07 (LA), 5.11 ± 0.12 (HS), 4.04 ± 0.06 (DR). For HS case at $m=5,7$ we find respectively $\mu = 5.86 \pm 0.14$ and 4.48 ± 0.08 . For HS and other species we have an average $B \approx 1$.

Usually for ingoing links distribution of WWW and other networks one finds the exponent $\tilde{\mu} \approx 2.1$ [23,24], [25]. This value of $\tilde{\mu}$ is expected to be the same as the exponent for ingoing matrix elements of matrix G . Indeed, for the ingoing matrix elements of Cambridge and Oxford networks we find respectively the exponents $\mu = 2.12 \pm 0.03$ and 2.06 ± 0.02 (see curves in Fig. 3). For ingoing links distribution of Cambridge and Oxford networks we obtain respectively $\tilde{\mu} = 2.29 \pm 0.02$ and $\tilde{\mu} = 2.27 \pm 0.02$ which are close to the usual WWW value $\tilde{\mu} \approx 2.1$. Thus we can say that for the WWW type networks we have $\mu \approx \tilde{\mu}$. In contrast the exponent μ for DNA Google matrix elements gets significantly

larger value $\mu \approx 5$. This feature marks a significant difference between DNA and WWW networks.

For DNA we see that there is a certain curvature in addition to a linear decay in log-log scale. From one side, all species are close to a unique universal decay curve which describes the distribution of ingoing matrix elements g_s (there is a more pronounced deviation for DR which does not belong to mammalian species). However, from other side we see visible differences between distributions of various species (e.g. non mammalian DR case has the largest deviation from others mammalian species). We will discuss the links between μ and the exponent β of PageRank algebraic decay $P(K) \propto 1/K^\beta$ in next sections.

Spectrum of DNA Google matrix

The spectrum of eigenstates of DNA Google matrix G of HS is shown in Fig. 4 for words of $m=5,6,7$ letters and matrix sizes $N=4^m$. The spectra for DNA sequences of bull BT, dog CF, elephant LA and zebrafish DR are shown in Fig. 5 for words of $m=6$ letters. The spectra and eigenstates are obtained by direct numerical diagonalization of matrix G using LAPACK standard code.

In all cases the spectrum has a large gap which separates eigenvalue $\lambda=1$ and all other eigenvalues with $|\lambda| < 0.5$ (only for non mammalian DR case we have a small group of eigenvalues within $0.5 < |\lambda| < 0.75$). This is drastically different from the spectrum of WWW and other type networks which usually have no gap in the vicinity of $\lambda=1$ (see e.g. [4,21], [22]). In a certain sense the DNA G spectrum is similar to the spectrum of randomized WWW networks and the spectrum of G of the Albert-Baraási network model discussed in [26], but the properties of the PageRank vector are rather different as we will see below.

Visually the spectrum is mostly similar between HS and CF having approximately the same radius of circular cloud $|\lambda| < \lambda_c \approx 0.2$. For DR this radius is the smallest with $\lambda_c \approx 0.1$. Thus the spectrum of G indicates the difference between mammalian and non mammalian sequences. For HS the increase of the word length $m=5;6;7$ leads to an increase of $\lambda_c \approx 0.1;0.2;0.35$. For $m=7$ the number of nonzero matrix elements G_{ij} is close to N^2 and thus on average we have only about $L/(mN^2) \approx 8$ transitions per each element. This determines an

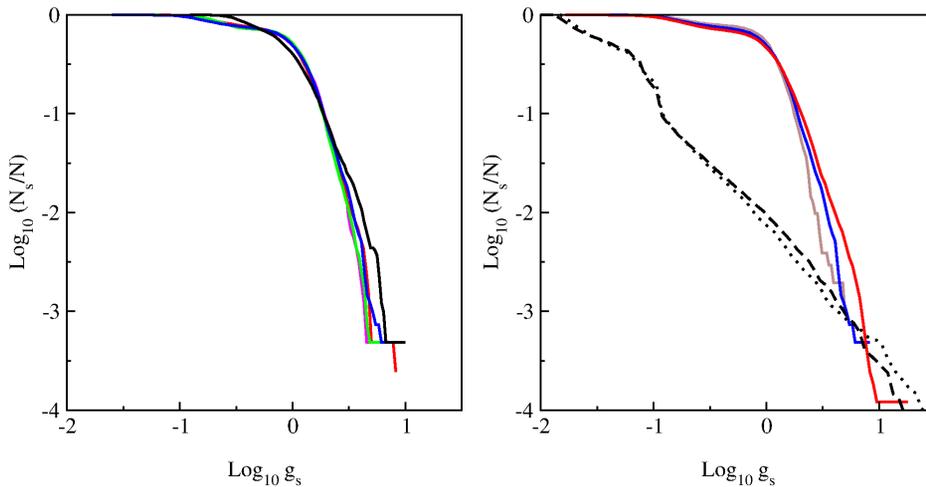


Figure 3. Integrated fraction N_s/N of sum of ingoing matrix elements with $\sum_{j=1}^N G_{ij} \geq g_s$. Left and right panels show the same cases as in Fig. 2 in same colors. The dashed and dotted curves are shifted in x -axis by one unit left to fit the figure scale. doi:10.1371/journal.pone.0061519.g003

approximate limit of reliable statistical computation of matrix elements G_{ij} for available HS sequence length L . For HS at $m=6$ we verified that two halves of the whole sequence L still give practically the same spectrum with a relative accuracy of

$\Delta\lambda/\lambda \approx 0.01$ for eigenvalues in the main part of the cloud at $\lambda_c/3 < |\lambda| < \lambda_c$. This means that the spectrum presented in Figs 4,5 is statistically stable at the values of L used in this work.

We also constructed the Google matrix G^* by inverting the direction of transitions $T_{ij} \rightarrow T_{ji}$ and then normalizing sum of all elements in each column to unity. This procedure is also equivalent to moving along the sequence, from word to word, not from left to right but from right to left. We note that for WWW and other networks such a matrix with inverted direction of links was used to obtain the CheiRank vector (which is the PageRank vector of matrix G^*). Due to the inversion of links the CheiRank vector highlights very communicative nodes [4,20], [21,22]. In our case the spectrum of G and G^* are identical. As a result the probability distributions of PageRank and CheiRank vectors are the same. This is due to some kind of detailed balance principle: we count only transitions between nearby words in a DNA sequence and the direction of displacement along the sequence does not affect the average transition probabilities so that $T_{ij} = T_{ji}$ (up to statistical fluctuations). In a certain sense this situation is similar to the case of Ulam networks in symplectic maps where the conservation of phase space area leads to the same properties of G and G^* [7,10].

We tried to test if a random matrix model can reproduce the distribution of eigenvalues in λ plane. With this aim we generated random matrix elements G_{ij} with exactly the same distribution N_g as for HS case at $m=6$ (see Fig. 2). However, in this random model we found all eigenvalues homogeneously distributed in the radius $\lambda_c \approx 0.07$ being significantly smaller compared to the real data. Also in this case the PageRank probability $P(K)$ changes only by 30% in the whole range $1 \leq K \leq N$ being absolutely different from the real data (see next section). Thus the construction of random matrix models which are able to produce results similar to the real data remains as a task for future investigations.

PageRank properties of various species

By numerical diagonalization of the Google matrix we determine the PageRank vector $P(K)$ at $\lambda=1$ and several other eigenvectors with maximal values of $|\lambda|$. The dependence of probability P on index K is shown in Fig. 6 for various species and different word length m . The probability $P(K)$ describes the steady

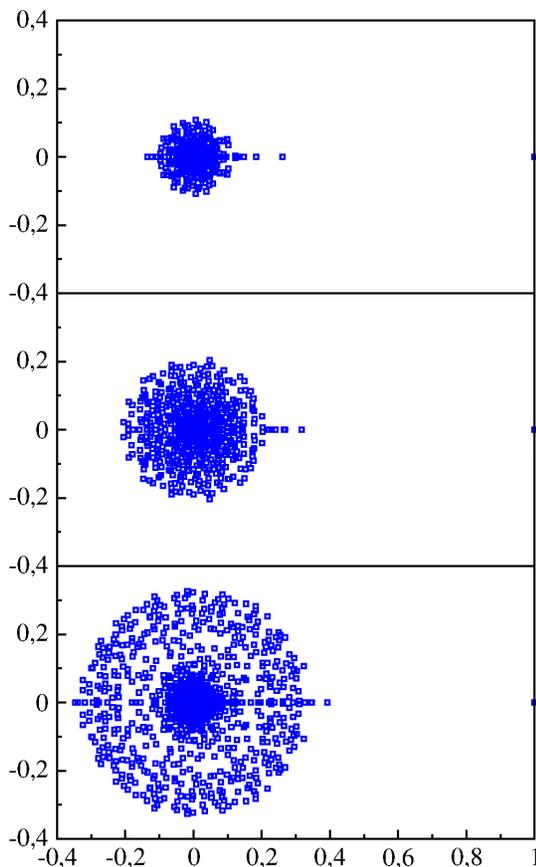


Figure 4. Spectrum of eigenvalues in the complex plane λ for DNA Google matrix of Homo sapiens (HS) shown for words of 5,6,7 letters (from top to bottom). doi:10.1371/journal.pone.0061519.g004

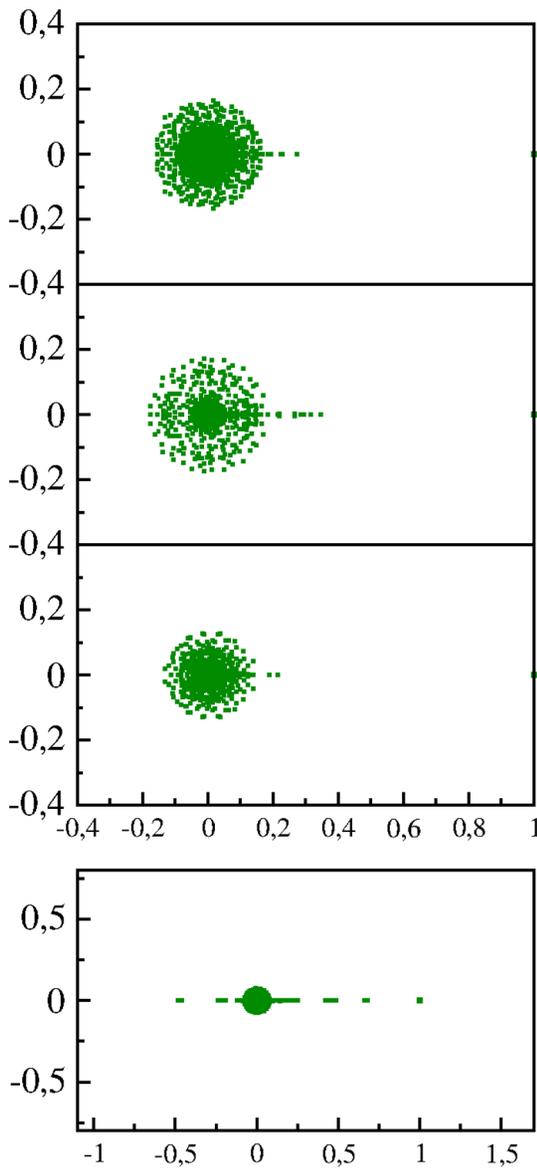


Figure 5. Spectrum of eigenvalues in the complex plane λ for DNA Google matrix of of bull BT, dog CF, elephant LA, zebrafish DR shown for words of 6 letters (from top to bottom). doi:10.1371/journal.pone.0061519.g005

state of random walks on the Markov chain and thus it gives the frequency of appearance of various words of length m in the whole sequence L . The frequencies or probabilities of words appearance in the sequences have been obtained in [13] by a direct counting of words along the sequence (the available sequences L were shorted at that times). Both methods are mathematically equivalent and indeed our distributions $P(K)$ are in a good agreements with those found in [13] even if now we have a significantly better statistics.

The decay of P with K can be approximately described by a power law $P \sim 1/K^\beta$. Thus for example for HS sequence at $m=7$ we find $\beta=0.357 \pm 0.003$ for the fit range $1.5 \leq \log_{10} K \leq 3.7$ that is rather close to the exponent found in [13]. Since on average the PageRank probability is proportional to the number of ingoing links, or the sum of ingoing matrix elements of G , one has the relation between the exponent of PageRank β and exponent of ingoing links (or matrix elements): $\beta=1/(\mu-1)$ [3,4], [23,24],

[25]. Indeed, for the HS DNA case at $m=7$ we have $\mu=4.48$ that gives $\beta=0.29$ being close to the above value of $\beta=0.357$ obtained from the direct fit of $P(K)$ dependence. We think that the agreement is not so perfect since there is a visible curvature in the log-log plot of N_s vs g_s in Fig. 3. Also due to a small value of β the variation range of P is not so large that reduces the accuracy of the numerical fit even if a formal statistical error is relatively small compared to a visible systematic nonlinear variations. In spite of this only approximate agreement we should say that in global the relation between β and μ works correctly. In average we find for DNA network the value of $\mu \approx 5$ being significantly larger than for the WWW networks with $\tilde{\mu} \approx 2.1$ [3]. This gives a significantly smaller value $\beta \approx 0.25$ for DNA case comparing to the usual WWW value $\beta \approx 0.9$ (we note that the randomized WWW networks and the Albert-Barabási model have $\beta \approx 1$ [26]). The relation between β and μ also works for the DR DNA case at $m=6$ with $\mu=4.04$ that gives $\beta=0.33$ being in a satisfactory agreement with the fit value $\beta=0.426$ found from $P(K)$ dependence of Fig. 6.

At $m=6$ we find for our species the following values of exponent $\beta=0.273 \pm 0.005$ (BT), 0.340 ± 0.005 (CF), 0.281 ± 0.005 (LA), 0.308 ± 0.005 (HS), 0.426 ± 0.008 (DR) in the range $1 \leq \log_{10} K \leq 3.3$. There is a relatively small variation of β between various mammalian species. The data of Fig. 6 for HS show that the value of β remains stable with the increase of word length. These observations are similar to those made in [13].

PageRank proximity between species

The top ten 6-letters words, with largest probabilities $P(K)$, are given for all studied species in Table 1. Two top words are identical for BT, CF, HS. To see a similarity between species on a global scale it is convenient to plot the PageRank index $K_s(i)$ of a given species s versus the index $K_{hs}(i)$ of HS for the same word i . For identical sequences one should have all points on diagonal, while the deviations from diagonal characterize the differences between species. The examples of such PageRank proximity $K-K$ diagrams are shown in Figs. 7,8 for words at $m=6$. A zoom of data on a small scale at the range $1 \leq K \leq 200$ is shown in Fig. 9. A visual impression is that CF case has less deviations from HS rank compared to BT and LA. The non-mammalian DR case has most strong deviations from HS rank. For BT, CF and LA cases we have a significant reduction of deviations from diagonal around $K \approx 3N/4$. This effect is also visible for DR case even if being less pronounced. We do not have explanation for this observation.

The fraction of purine letters A or G in a word of $m=6$ letters is shown by color in Fig. 7 for all words ranked by PageRank index K . We see that these letters are approximately homogeneously distributed over the whole range of K values. In contrast to that the distribution of letters A or T is inhomogeneous in K : their fraction is dominant for $1 \leq K < N/4$, approximately homogeneous for $N/4 \leq K \leq 3N/4$ and is close to zero for $3N/4 < K \leq N$ (see Fig. 8). We find that in the whole HS sequence the fractions $F_{a,c,g,t}$ of A, C, G, T are respectively $0.276596, 0.192576, 0.192624, 0.276892$ (and $F_n=0.061312$ for undetermined N). Thus we have the fraction of A, G being close to $1/2 \approx (F_a + F_g)/(1 - F_n) = 0.499867$ and the fraction of A, T being $(F_a + F_t)/(1 - F_n) = 0.589640 > 0.5$. Thus it is more probable to have A or T in the whole sequence that can be a possible origin of the inhomogeneous distribution of A or T along K and large fraction of A, T at top PageRank positions.

The whole HS sequence used here is composed from 5 humans with individual length $L_i \approx 3 \cdot 10^9 \approx L/5$. We consider the first and last fifth parts of the whole sequence L separately thus forming two independent sequences HS1 and HS2 of two individuals. We

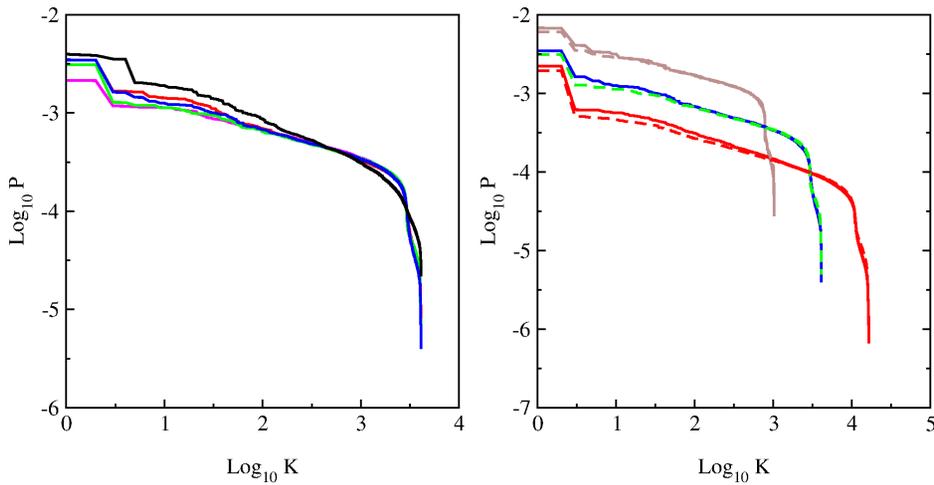


Figure 6. Dependence of PageRank probability $P(K)$ on PageRank index K . *Left panel* : Data for different species for word length of 6-letters: bull BT (magenta), dog CF (red), elephant LA (green), Homo sapiens HS (blue) and zebrafish DR (black). *Right panel* : Data for HS (full curve) and LA (dashed curve) for word length $m=5$ (brown), 6 (blue/green), 7 (red). doi:10.1371/journal.pone.0061519.g006

determine for the the corresponding PageRank indexes K_{hs1} and K_{hs2} and show their PageRank proximity diagram in Fig. 10. In this case the points are much closer to diagonal compared to the case of comparison of HS with other species.

To characterize the proximity between different species or different HS individuals we compute the average dispersion $\sigma(s_1, s_2) = \sqrt{\sum_{i=1}^N (K_{s_1}(i) - K_{s_2}(i))^2} / N$ between two species (individuals) s_1 and s_2 . Comparing the words with length $m = 5, 6, 7$

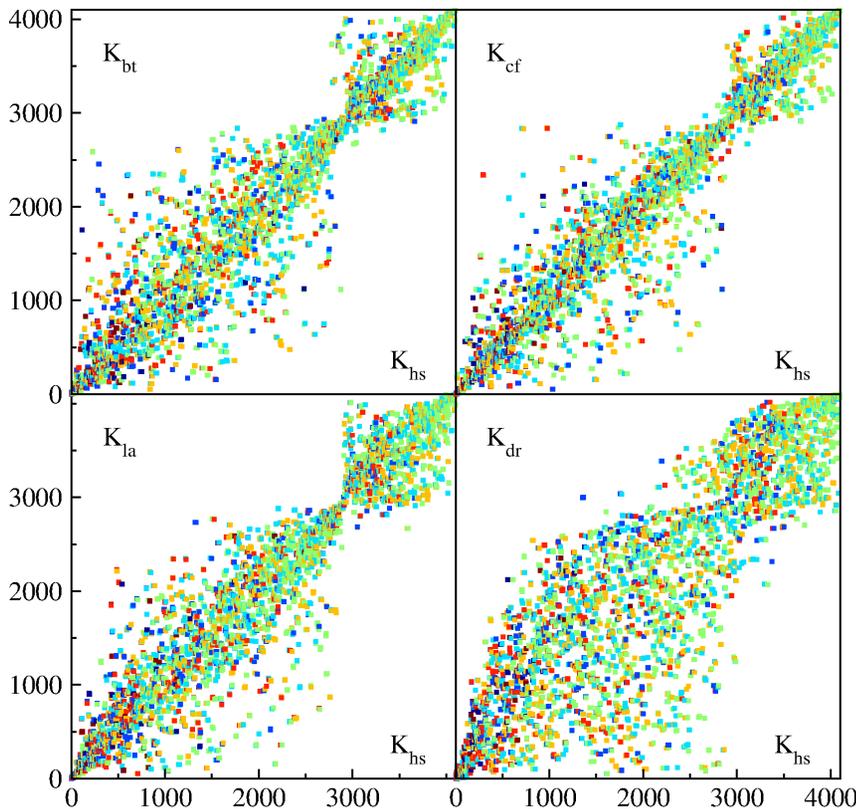


Figure 7. PageRank proximity $K - K$ plane diagrams for different species in comparison with Homo sapiens: *x-axis* shows PageRank index $K_{hs}(i)$ of a word i and *y-axis* shows PageRank index of the same word i with $K_{bt}(i)$ of bull, $K_{cf}(i)$ of dog, $K_{la}(i)$ of elephant and $K_{dr}(i)$ of zebrafish; here the word length is $m=6$. The colors of symbols marks the purine content in a word i (fractions of letters A or G in any order); the color varies from red at maximal content, via brown, yellow, green, light blue, to blue at minimal zero content. doi:10.1371/journal.pone.0061519.g007

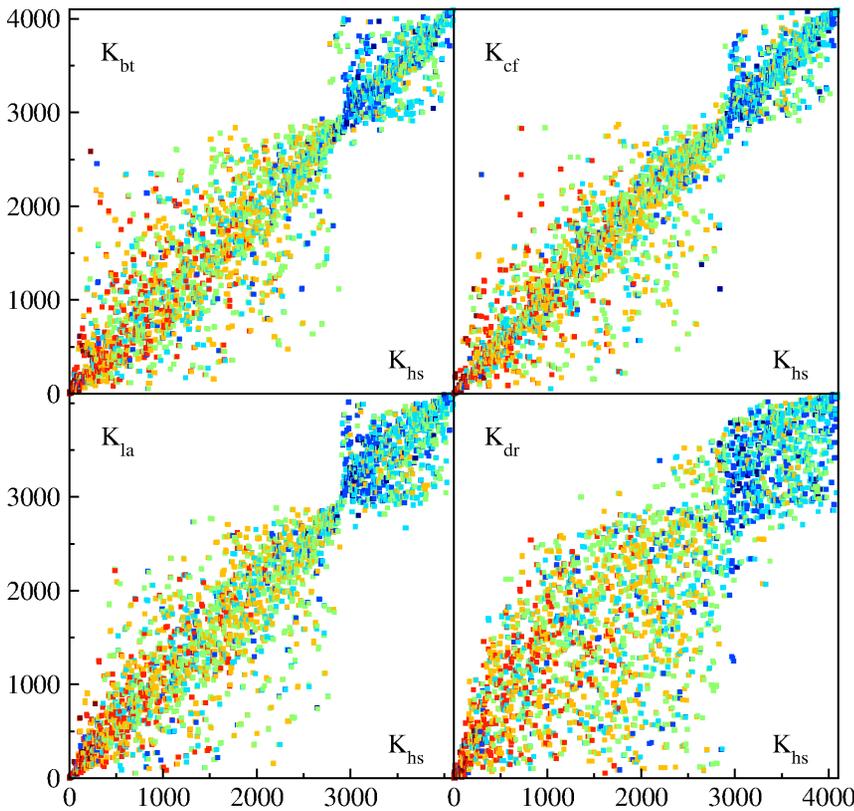


Figure 8. Same as in Fig. 7 but now the color marks the fraction of letters A or T in any order in a word i with red at maximal content and blue at zero content.
doi:10.1371/journal.pone.0061519.g008

we find that the scaling $\sigma \propto N$ works with a good accuracy (about 10% when N is increased by a factor 16). To represent the result in a form independent of m we compare the values of σ with the corresponding random model value σ_{rnd} . This value is computed assuming a random distribution of N points in a square $N \times N$ when only one point appears in each column and each line (e.g. at $m=6$ we have $\sigma_{rnd} \approx 1673$ and $\sigma_{rnd} \propto N$). The dimensionless dispersion is then given by $\zeta(s_1, s_2) = \sigma(s_1, s_2) / \sigma_{rnd}$. From the ranking of different species we obtain the following values at $m=6$: $\zeta(CF, BT) = 0.308$; $\zeta(LA, BT) = 0.324$, $\zeta(LA, CF) = 0.303$; $\zeta(HS, BT) = 0.246$, $\zeta(HS, CF) = 0.206$, $\zeta(HS, LA) = 0.238$; $\zeta(DR, BT) = 0.425$, $\zeta(DR, CF) = 0.414$, $\zeta(DR, LA) = 0.422$, $\zeta(DR, HS) = 0.375$ (other m have similar values). According to this statistical analysis of PageRank proximity between species we find that ζ value is minimal between CF and HS showing that these are two most similar species among those considered here.

For two HS individuals we find $\zeta(HS1, HS2) = 0.031$ being significantly smaller than the proximity correlator between different species. We think that this PageRank proximity correlator ζ can be useful as a quantitative measure of statistical proximity between various species.

Finally, in Table 2 we give for all species the words of 6 letters with the 10 minimal PageRank probabilities. Thus for HS the less probable is the word TACGCG corresponding to two amino acids Tyr and Ala. In general the ten last words are mainly composed of C and G even if the letters A and T still have small but nonzero weight. The last two words are the same for mammalian species but they are different for DR sequence.

Other eigenvectors of G

The properties of 10 eigenstates $\psi_i(j)$ of DNA Google matrix with largest modulus of eigenvalues $|\lambda_i|$ are analyzed in Table 3 and Fig. 11. The words W_i at the maximal amplitude $|\psi_i(j)|$ are presented for all species in Table 3. We see that in general these words W_i are rather different from the top PageRank word W_1 (some words appear in pairs since there are pairs of complex conjugated values $\lambda_i = \lambda_i^*$).

The probability of the above top 10 eigenstates as a function of PageRank index K are shown in Fig. 11. We see that the majority of the vectors, different from the PageRank vector, have well localized peaks at relatively large values $K > 50$. This shows that in the DNA network there are some modes located on certain specific patterns of words.

To illustrate the localized structure of eigenmodes $\psi_i(j)$ for HS case at $m=6$ we compute the inverse participation ratio $\xi_i = (\sum_j |\psi_i(j)|^2)^2 / \sum_j |\psi_i(j)|^4$ which gives an approximate number of nodes on which the main probability of an eigenstate $\psi_i(j)$ is located (see e.g. [4,21,26]). The obtained values are $\xi_i = 385.26, 16.37, 2.07, 1.72, 2.23, 3.19, 77.43, 77.43, 2.33, 2.06$ for $i=1, \dots, 10$ respectively. We see that for $i > 1$ we have significantly smaller ξ values compared to the case of PageRank vector with a large ξ_1 . This supports the conclusion about localized structure of a large fraction of eigenvectors of G .

In [22] on an example of Wikipedia network it is shown that the eigenstates with relatively large $|\lambda|$ select specific communities of the network. The detection of communities in complex networks is now an active research direction [27]. We expect that the eigenmodes of G matrix can select specific words of bioniformatic

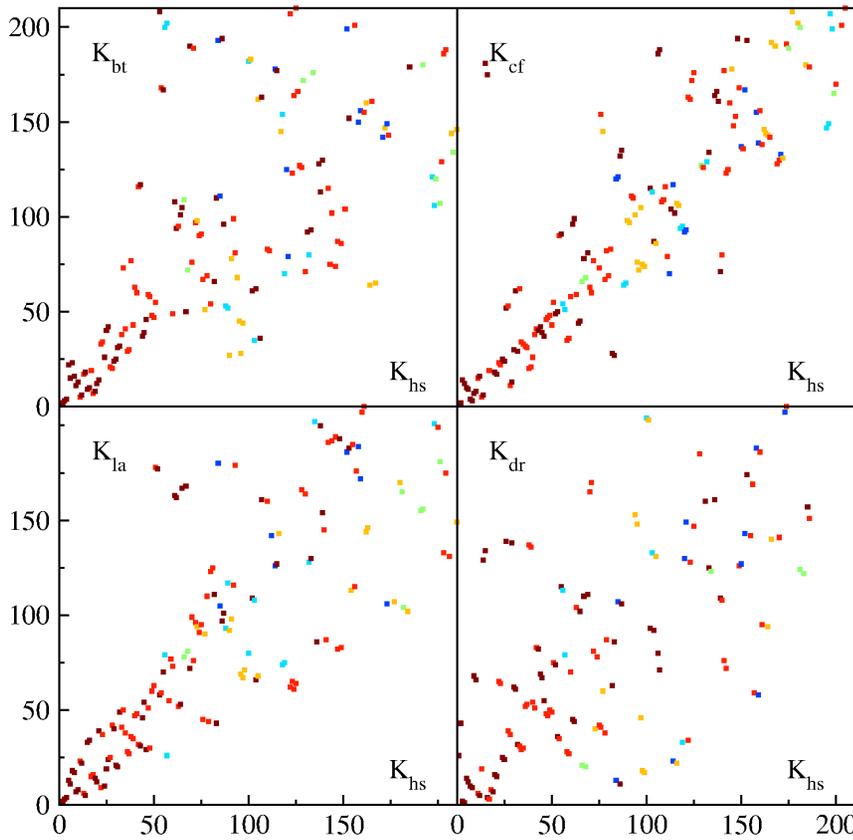


Figure 9. Zoom of the PageRank proximity $K-K$ diagram of Fig. 8 for the range $1 \leq K \leq 200$ with the same color for A or T content.
doi:10.1371/journal.pone.0061519.g009

interest. However, a detailed analysis of words from eigenmodes remains for further more detailed investigations.

Discussion

In this work we used long DNA sequences of various species to construct from them the Markov process describing the probabilistic transitions between words of up to 7 letters length. We construct the Google matrix of such transitions with the size up to

4^7 and analyze the statistical properties of its matrix elements. We show that for all 5 species, studied in this work, the matrix elements of significant amplitude have a power law distribution with the exponent $\nu \approx 2.5$ being close to the exponent of outgoing links distribution typical for WWW and other complex directed networks with $\tilde{\nu} \approx 2.7$. The distribution of significant values of the sum of ingoing matrix elements of G is also described by a power

Table 1. Top ten PageRank entries at DNA word length $m = 6$ for species: bull BT, dog CF, elephant LA, Homo sapiens HS and zebrafish DR.

| BT | CF | LA | HS | DR |
|--------|--------|--------|--------|--------|
| TTTTTT | TTTTTT | AAAAAA | TTTTTT | ATATAT |
| AAAAAA | AAAAAA | TTTTTT | AAAAAA | TATATA |
| ATTTTT | AATAAA | ATTTTT | ATTTTT | AAAAAA |
| AAAAAT | TTTATT | AAAAAT | AAAAAT | TTTTTT |
| TTCTTT | AAATAA | AGAAAA | TATTTT | AATAAA |
| TTTTAA | TTATTT | TTTTCT | AAAATA | TTTATT |
| AAAGAA | AAAAAT | AAGAAA | TTTTTA | AAATAA |
| TTAAAA | ATTTTT | TTTCTT | TAAAAA | TTATTT |
| TTTTCT | TTTTTA | TTTTTA | TTATTT | CACACA |
| AGAAAA | TAAAAA | TAAAAA | AAATAA | TGTGTG |

doi:10.1371/journal.pone.0061519.t001

Table 2. Ten words with minimal PageRank probability given at $m = 6$ for species: bull BT, dog CF, elephant LA, Homo sapiens HS and zebrafish DR.

| BT | CF | LA | HS | DR |
|---------|---------|--------|---------|---------|
| CGCGTA | TACGCG | CGCGTA | TACGCG | CCGACG |
| TACGCG | CGCGTA | TACGCG | CGCGTA | CGTCGG |
| CGTACG | TCGCGA | ATCGCG | CGTACG | CGTCGA |
| CGATCG | CGTACG | TCGCGA | TCGACG | TCGACG |
| ATCGCG | CGATCG | CGCGAT | CGTCGA | TCGTCTG |
| CGCGAT | CGAACG | GTCGCG | CGATCG | CCGTCTG |
| TCGACG | CGTTCTG | CGATCG | CGTTCTG | CGACGG |
| CGTCGA | TCGACG | CGCGAC | CGAACG | CGACCG |
| CGTTCTG | CGTCGA | TCGCGC | CGACGA | CGGTCTG |
| TCGTCTG | ACGCGA | ACGCGA | CGCGAA | CGACGA |

Here the top row is the last PageRank entry, bottom is the tenth one from the end of PageRank.

doi:10.1371/journal.pone.0061519.t002

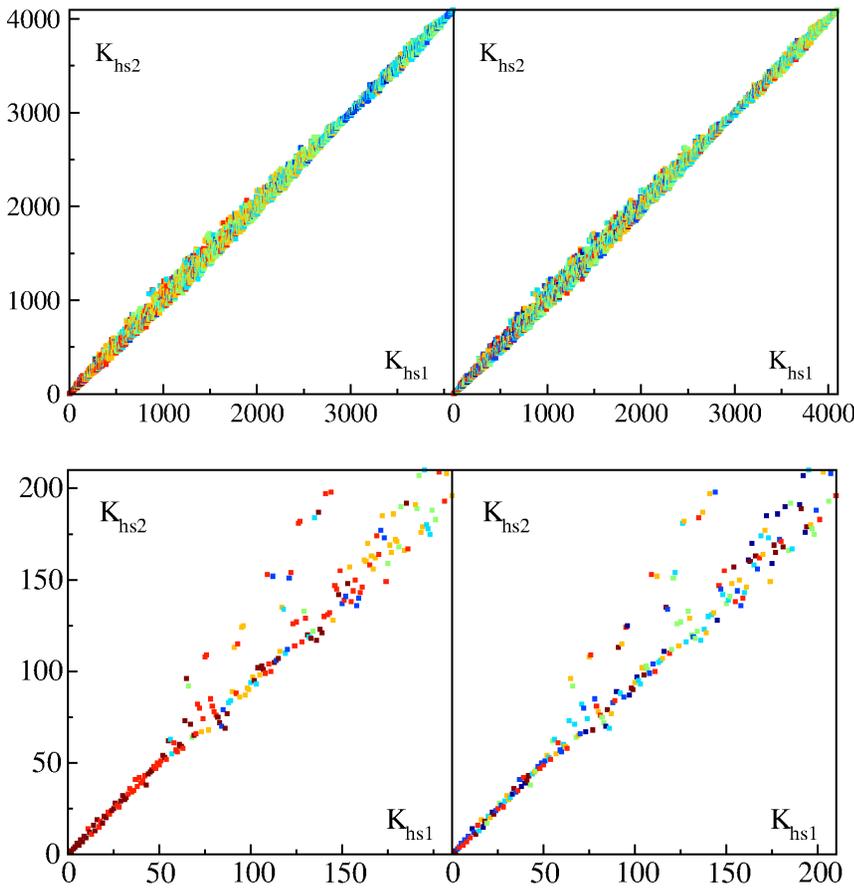


Figure 10. PageRank proximity $K-K$ diagram of Homo sapiens HS2 versus Homo sapiens HS1 at $m=6$ (see text for details). Top panels show the content of A, T (left) and A, G (right) in the same way as in Fig. 8 and Fig. 7 respectively. Bottom panels show zoom of top panels. doi:10.1371/journal.pone.0061519.g010

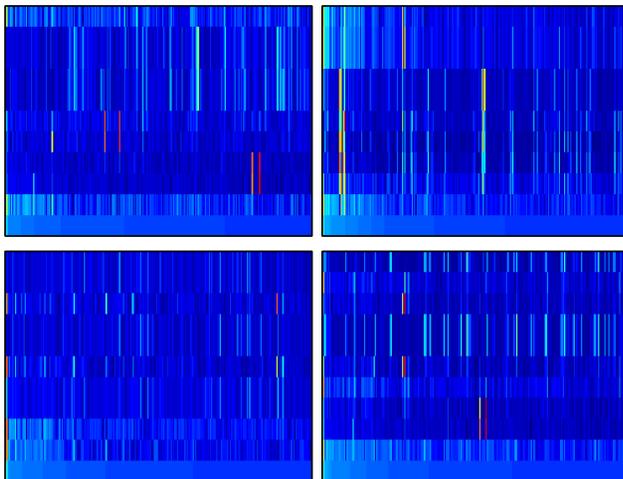


Figure 11. Dependence of eigenstates amplitude $|\psi_i(K)|$ on PageRank index K in x -axis and eigenvalue index i in y -axis for largest ten eigenvalues $|\lambda_i|$ counted by i from $i=1$ at $|\lambda_1|=1$ to $i=10$ at $|\lambda_{10}|\approx 0.2$. The range $1\leq K\leq 250$ is shown with PageRank vector for a given species at the bottom line of each panel. For each species in each panel the color is proportional to $\sqrt{|\psi_i(j)|}$ changing from blue at zero to red at maximal amplitude value which is close to unity in each panel. The panels show the species: bull BT (top left), dog CF (top right), elephant LA (bottom left), Homo sapiens HS (bottom right). doi:10.1371/journal.pone.0061519.g011

Table 3. Words W_i corresponding to the maximum value of eigenvector modulus $w_i = \max_j(|\psi_i(j)|)$ for species bull BT, dog CF, elephant LA, Homo sapiens HS and zebrafish DR, which are shown in dark red in Fig. 11.

| i | BT | CF | LA | HS | DR |
|-----|--------|--------|--------|--------|--------|
| 1 | TTTTTT | TTTTTT | AAAAAA | TTTTTT | ATATAT |
| 2 | TTTTTT | AAAAAA | AAAAAA | TTTTTT | TATATA |
| 3 | ACACAC | CTCTCT | AAAAAA | ACACAC | ATATAT |
| 4 | ACACAC | AGAGAG | AAAAAA | ACACAC | TAGATA |
| 5 | CACACA | CTCTCT | AAAAAA | TTTTTT | ATAGAT |
| 6 | CACACA | TCTCTC | AAAAAA | CACACA | TATCTA |
| 7 | CCAGGC | AGAGAG | TATGAG | TGGGAG | ATCTAT |
| 8 | CCAGGC | AGAGAG | TATGAG | TGGGAG | TAGATA |
| 9 | CCCATG | TGTGTG | TTTTTT | CACACA | ATAGAT |
| 10 | CCCATG | TGTGTG | AGAGTA | TTTTTT | TATCTA |

The eigenvectors at $i=1, \dots, 10$ correspond to the ten largest eigenvalues $|\lambda_1|, \dots, |\lambda_{10}|$ of the DNA Google matrix for DNA word length $m=6$. The first row $i=1$ corresponds to top PageRank entries. doi:10.1371/journal.pone.0061519.t003

law with the exponent $\mu \approx 5$ which is significantly larger than the corresponding exponent for WWW networks with $\mu \approx 2.1$. We show that similar to the WWW networks the exponent μ determines the exponent $\beta = 1/(\mu - 1) \approx 0.25$ of the algebraic PageRank decay which is significantly smaller than its value for WWW networks with $\beta \approx 0.9$. The PageRank decay is similar to the frequency decay of various words studied previously in [13]. It is interesting to note that the value $\mu - 1$ is close to the exponent of Poincaré recurrences decay which has a value close to 4 [12] (even if we cannot derive a direct mathematical relation between them).

Using PageRank vectors of various species we introduce the PageRank proximity correlator ζ which allows to measure in a quantitative way the proximity between different species. This parameter remains stable in respect to variation of the word length.

The spectrum of the Google matrix is determined and it is shown that it is characterized by a significant gap between $\lambda = 1$ and other eigenvalues. Thus, this spectrum is qualitatively different from the WWW case where the gap is absent at the damping factor $\alpha = 1$. We show that the eigenmodes with largest values of $|\lambda| < 1$ are well localized on specific words and we argue that the words corresponding to such localized modes can play an interesting role in bioinformatic properties of DNA sequences.

Finally we would like to trace parallels between the Google matrix analysis of words in DNA sequences and the small world properties of human language. Indeed, it is known that the frequency of words in natural languages follows a power law Zipf distribution with the exponent $\beta \approx 1$ [28]. The parallels between words distributions in DNA sequences and statistical linguistics were already pointed in [13]. The analysis of degree distributions of undirected networks of words in natural languages was found to follow a power law with an exponent $\nu_l \approx 1.5 - 2.7$ [29] being not

so far from the one found here for the matrix elements distribution. It is argued that the language evolution plays an important role in the formation of such a distribution in languages [30]. The parallels between linguistics and DNA sequence complexity are actively discussed in bioinformatics [31,32]. We think that the Google matrix analysis can provide new insights in the construction and characterization of information flows on DNA sequence networks extending recent steps done in [33].

In summary, our results show that the distributions of significant matrix elements are similar to those of the scale-free type networks like WWW, Wikipedia and linguistic networks. In analogy with linguistic networks it can be useful to go from words network analysis to a more advanced functional level of links inside sentences that may be viewed as a network of links between amino acids or more complex biological constructions.

Supporting Information

Supporting Information S1. Supplementary methods, references, tables, sequences data and figures are available at: <http://www.quantware.ups-tlse.fr/QWLIB/dnagooglematrix/>.

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Author Contributions

Conceived and designed the experiments: DLS. Performed the experiments: VK. Analyzed the data: VK DLS. Contributed reagents/materials/analysis tools: VK DLS. Wrote the paper: VK DLS.

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