

Markov chain order estimation with parametric significance tests of conditional mutual information

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Abstract

Besides the different approaches suggested in the literature, accurate estimation of the order of a Markov chain from a given symbol sequence is an open issue, especially when the order is moderately large. Here, parametric significance tests of conditional mutual information (CMI) of increasing order m , $I_c(m)$, on a symbol sequence are conducted for increasing orders m in order to estimate the true order L of the underlying Markov chain. CMI of order m is the mutual information of two variables in the Markov chain being m time steps apart, conditioning on the intermediate variables of the chain. The null distribution of CMI is approximated with a normal and gamma distribution deriving analytic expressions of their parameters, and a gamma distribution deriving its parameters from the mean and variance of the normal distribution. The accuracy of order estimation is assessed with the three parametric tests, and the parametric tests are compared to the randomization significance test and other known order estimation criteria using Monte Carlo simulations of Markov chains with different order L , length of symbol sequence N and number of symbols K . The parametric test using the gamma distribution (with directly defined parameters) is consistently better than the other two parametric tests and matches well the performance of the randomization test. The tests are applied to genes and intergenic regions of DNA sequences, and the estimated orders are interpreted in view of the results from the simulation study. The application shows the usefulness of the parametric gamma test for long symbol sequences where the randomization test becomes prohibitively slow to compute.

Keywords: Symbol sequence, Markov chain order, conditional mutual information, significance test, DNA

1. Introduction

Symbol sequences are directly observed on real-world processes, such as DNA sequences and on-line transaction logs, but can also be derived from discretization of

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time series. Sequence analysis, initially developed mostly for biological applications [1], has expanded with regard to both applications and methodologies, and sequence mining techniques are constantly being developed [2]. Here however, we concentrate on a classical and fundamental problem that regards the memory of the underlying mechanism to a symbol sequence. In the presence of association in symbol sequences, the first step of the analysis is to assume a Markov chain and estimate the order of the Markov chain.

There are many Markov chain order estimators proposed and assessed in the literature. The Bayesian information criterion (BIC) and the Akaike information criterion (AIC) are the two oldest and best known order estimators based on maximum likelihood [3, 4, 5]. Another estimator is given by the maximal fluctuation method proposed by Peres-Shields [6] and modified by Dalevi and Dubhashi [7], who found that the Peres-Shields (PS) estimator is simpler, faster and more robust to noise than other criteria like AIC and BIC [7]. Other order estimation schemes include the method of Menéndez et al. [8], which uses the ϕ -divergence measures [9], the method of global dependency level (GDL), also called relative entropy [10], and the efficient determination criterion (EDC) [11]. Based on the information-related measures, and specifically the conditional mutual information (CMI), we recently proposed the order estimation by means of randomization significance tests for CMI at increasing orders [12]. In a somewhat similar way, Pethel et al. [13] propose a randomization test for the examined Markov chain order using the Chi-squared statistic.

In the approach of [12] we made no assumption on the distribution of CMI. Here we propose the order estimation with parametric tests, approximating the null distribution of CMI by normal and gamma distributions. We follow the bias correction and the approximation for the variance in [14] and [15] and approximate the distribution of mutual information with Gaussian distribution as an obvious possible choice [16, 17]. We also consider the result in Goebel et al. [18] that the statistic of mutual information (MI), and subsequently CMI, follows gamma distribution. Finally, we consider a second gamma approximation with shape and scale parameter derived from the mean and variance approximations of the normal distribution. We implement the three parametric significance tests for CMI and compare them to the randomization test of [12], as well as other known Markov chain order estimation methods. Further, we attempt to assess the Markov chain order of DNA sequences and infer for short and long range correlation on the basis of the parametric and randomization CMI testing. A systematic investigation of long range correlation of DNA sequences using the CMI approach is reported in [19].

The structure of the paper is as follows. First, in Section 2, CMI is defined and estimated on symbol sequences. Parametric significance tests for CMI of increasing orders are presented, approximating the null distribution of CMI by the normal and gamma distributions. In Section 3, we assess the efficiency of the parametric tests in estimating the Markov chain orders and compare them to other known methods. In Section 4, we apply the parametric and randomization tests to DNA sequences, and in Section 5, the results are discussed and the main conclusions are drawn.

2. Conditional Mutual Information and Markov Chain Order Estimation

We start with the definition of entropy, mutual information (MI) and conditional mutual information (CMI) for Markov chains. Let $\{x_t\}$ denote a symbol sequence generated by a Markov chain $\{X_t\}$, $t \geq 1$, of an unknown order $L \geq 1$ in a discrete space of K possible states $A = \{a_1, \dots, a_K\}$, $p(x_t)$ the probability of $x_t \in A$ occurring in the chain, $\mathbf{X}_t = [X_t, X_{t-1}, \dots, X_{t-m+1}]$ a vector (word) of m successive variables of the Markov chain and $p(\mathbf{x}_t)$ the probability of a word $\mathbf{x}_t = \{x_t, x_{t-1}, \dots, x_{t-m+1}\} \in A^m$ occurring in the chain. The entropy of a random variable of the Markov chain X_t is $H(X_t) = -\sum_{x_t} p(x_t) \ln p(x_t)$ and the entropy of a word \mathbf{X}_t is $H(\mathbf{X}_t) = -\sum_{x_t, \dots, x_{t-m+1}} p(\mathbf{x}_t) \ln p(\mathbf{x}_t)$. The MI of two random variables in the Markov chain being m time steps apart is [20]

$$\begin{aligned} I(m) &= I(X_t; X_{t-m}) = H(X_t) + H(X_{t-m}) - H(X_t, X_{t-m}) \\ &= \sum_{x_t, x_{t-m}} p(x_t, x_{t-m}) \ln \frac{p(x_t, x_{t-m})}{p(x_t)p(x_{t-m})} \end{aligned}$$

and quantifies the amount of information for the one variable given the other variable.

The fundamental property of a Markov chain of order L is

$$p(X_t | X_{t-1}, X_{t-2}, \dots, X_{t-L}, X_{t-L-1}, \dots) = p(X_t | X_{t-1}, X_{t-2}, \dots, X_{t-L}), \quad (1)$$

meaning that the distribution of the variable X_t of the Markov chain at time t is determined only in terms of the preceding L variables of the chain. It is noted that $I(m)$ for $m > L$ may not drop to zero due to the existence of MI between the intermediate variables. Thus for estimating L we consider CMI that accounts for the intermediate variables. CMI of order m is defined as the mutual information of X_t and X_{t-m} conditioning on $X_{t-m+1}, \dots, X_{t-1}$ [20]

$$\begin{aligned} I_c(m) &= I(X_t; X_{t-m} | X_{t-1}, \dots, X_{t-m+1}) \\ &= -H(X_t, \dots, X_{t-m}) + H(X_{t-1}, \dots, X_{t-m}) + H(X_t, \dots, X_{t-m+1}) - H(X_{t-1}, \dots, X_{t-m+1}) \\ &= \sum_{x_t, \dots, x_{t-m}} p(x_t, \dots, x_{t-m}) \ln \frac{p(x_t | x_{t-1}, \dots, x_{t-m})}{p(x_t | x_{t-1}, \dots, x_{t-m+1})}. \end{aligned} \quad (2)$$

CMI coincides with MI for successive random variables in the chain, $I_c(1) = I(1)$.

From the Markov chain property in (1), for $m > L$ the logarithmic term in the sum of (2) is zero and thus $I_c(m) = 0$. On the other hand, for $m \leq L$, we expect in general the two variables m time steps apart be dependent given the $m - 1$ intermediate variables, and $I_c(m) > 0$. It is possible that $I_c(m) = 0$ for $m < L$, but not for $m = L$, as then the Markov chain order would not be L . So, increasing the order m , we expect in general when $I_c(m) > 0$ and $I_c(m+1) = 0$ to have $m = L$. To account for complicated and rather unusual cases where $I_c(m+1) = 0$ occurs for $m+1 < L$, we can extend the condition $I_c(m) > 0$ and $I_c(m+1) = 0$ to require also $I_c(m+2) = 0$, and even further up to some maximum order.

2.1. Parametric tests for Markov chain order estimation

The estimate of entropy, MI and CMI from a symbol sequence $\{x_t\}_{t=1}^N$ of length N is derived directly by the maximum likelihood estimate of the probabilities given

simply by the relative frequencies. As entropy and MI are fundamental quantities of information theory with many applications, there is rich literature about the statistical properties and distribution of their estimates. Some works have focused on correcting the bias in the estimation of entropy [14, 21, 22, 15, 23, 16, 24, 25], whereas other works give approximations with parametric distributions [26, 27, 15, 18, 17]. For example, Roulston [15] estimates the bias and variance of the observed entropy and gives evidence for normal distribution of the estimates. Pardo [26] shows that, under different assumptions, the MI estimate is either normal or a linear combination of χ^2 variables, while Goebel et al. [18] using a second-order Taylor approximation of the MI estimate derives a gamma distribution, and the same does for CMI. Hutter and Zaffalon [17] use a Bayesian framework with Dirichlet prior distribution to obtain the posterior distribution of MI estimate and derive expressions for its mean and variance.

For simplicity in the expressions below, we assign X for X_t , Y for X_{t-m} and Z for the vector variable of $X_{t-1}, \dots, X_{t-m+1}$. The number of observed distinct symbols of X and Y are K but for Z there may be less observed distinct words than K^{m-1} denoted K_Z . Similarly, K_{XZ} , K_{YZ} and K_{XYZ} denote the number of observed distinct words concatenating the respective indexed variables. Note that the words XZ and YZ correspond to $X_t, X_{t-1}, \dots, X_{t-m+1}$ and $X_{t-1}, \dots, X_{t-m+1}, X_{t-m}$, respectively, and therefore we have $K_{XZ} = K_{YZ}$ (discrepancy by one may occur due to edge effect). Further, we denote $N_m = N - m$.

2.1.1. Approximation with normal distribution (ND)

An expression for the mean of the entropy estimate $\hat{H}(X)$, $\langle \hat{H}(X) \rangle$, is given by the bias correction of Miller [14]

$$\langle \hat{H}(X) \rangle = H(X) - \frac{K-1}{2N}. \quad (3)$$

The same expression holds for vector variables (words) adjusting accordingly the number of observed distinct words. The mean of the CMI estimate $\hat{I}_c(m)$ can thus be derived by substituting the mean of entropy estimates of (3) in the expression of CMI of (2)

$$\langle \hat{I}_c(m) \rangle = I_c(m) + \frac{K_{XYZ} - K_{ZX} - K_{YZ} + K_Z}{2N_m}. \quad (4)$$

For the CMI variance, we follow the variance approximation for MI in [15]. We start with the error propagation formula for $\hat{I}_c(m)$

$$V[\hat{I}_c(m)] = \sum_{u=1}^K \sum_{v=1}^K \sum_{w=1}^{K_Z} \left(\frac{\partial \hat{I}_c(m)}{\partial n_{uvw}} \right)^2 V[n_{uvw}], \quad (5)$$

where $V[\cdot]$ denotes the variance and n_{uvw} is the frequency of the concatenated word of XYZ that corresponds to the indices uvw . We want to express $\hat{I}_c(m)$ in (5) in terms of the observed probabilities (relative frequencies) of joints words of XYZ , $q_{ijk} = n_{ijk}/N_m$, and the marginal probabilities, e.g. $q_{\cdot jk} = \sum_{i=1}^K q_{ijk}$ and $q_{\cdot \cdot k} = \sum_{i=1}^K \sum_{j=1}^{K_Z} q_{ijk}$. Substituting these probabilities in the four entropy terms in (2) we get

$$\hat{I}_c(m) = \sum_{i=1}^K \sum_{j=1}^{K_Z} \sum_{k=1}^{K_Z} q_{ijk} \ln q_{ijk} - \sum_{i=1}^K \sum_{k=1}^{K_Z} q_{i\cdot k} \ln q_{i\cdot k} - \sum_{j=1}^{K_Z} \sum_{k=1}^{K_Z} q_{\cdot jk} \ln q_{\cdot jk} + \sum_{k=1}^{K_Z} q_{\cdot \cdot k} \ln q_{\cdot \cdot k}. \quad (6)$$

Differentiation of the observed joint and marginal probabilities in (6) with respect to n_{uvw} gives the following expressions

$$\frac{\partial q_{ijk}}{\partial n_{uvw}} = -\frac{n_{ijk}}{N_m^2} + \frac{\delta_{iu}\delta_{jv}\delta_{kw}}{N_m}, \quad (7)$$

$$\frac{\partial q_{\cdot jk}}{\partial n_{uvw}} = -\frac{1}{N_m^2} \sum_{i=1}^K n_{ijk} + \frac{\delta_{jv}\delta_{kw}}{N_m}, \quad (8)$$

$$\frac{\partial q_{i\cdot k}}{\partial n_{uvw}} = -\frac{1}{N_m^2} \sum_{j=1}^K n_{ijk} + \frac{\delta_{iu}\delta_{kw}}{N_m}, \quad (9)$$

$$\frac{\partial q_{\cdot\cdot k}}{\partial n_{uvw}} = -\frac{1}{N_m^2} \sum_{i=1}^K \sum_{j=1}^K n_{ijk} + \frac{\delta_{kw}}{N_m}, \quad (10)$$

where δ_{mn} is the Kronecker delta defined as $\delta_{mn} = 1$ when $m = n$ and $\delta_{mn} = 0$ when $m \neq n$. Substitution of (7-10) into (5) gives

$$V[\hat{I}_c(m)] = \sum_{u=1}^K \sum_{v=1}^K \sum_{w=1}^{K_z} \frac{1}{N_m^2} \left(-\ln q_{uvw} + \ln q_{u\cdot w} + \ln q_{\cdot v w} - \ln q_{\cdot\cdot w} + \hat{I}_c \right)^2 V[n_{uvw}].$$

The observed frequency n_{uvw} of the concatenated word of XYZ is itself a binomial random variable, $n_{uvw} \sim B(N_m, q_{uvw})$, considering the occurrence of the word as success with probability q_{uvw} and as number of trials the number N_m of possible words of length m in the symbol sequence. Thus the variance of n_{uvw} is $V[n_{uvw}] = N_m q_{uvw} (1 - q_{uvw})$ and substituting it in the expression above we have the final expression of the variance of \hat{I}_c

$$V[\hat{I}_c(m)] = \sum_{u=1}^K \sum_{v=1}^K \sum_{w=1}^{K_z} \frac{1}{N_m} \left(-\ln q_{uvw} + \ln q_{u\cdot w} + \ln q_{\cdot v w} - \ln q_{\cdot\cdot w} + \hat{I}_c \right)^2 q_{uvw} (1 - q_{uvw}). \quad (11)$$

Thus $V[\hat{I}_c(m)]$ is directly derived when the observed probabilities q_{uvw} are first computed on the symbol sequence.

In [15], similar expressions for the mean and variance of $I(m)$ were derived to define the normal approximation of the MI distribution. Similarly, we assume that the distribution of CMI follows approximately the normal distribution (denoted hereafter ND)

$$\hat{I}_c(m) \sim N_m(\langle \hat{I}_c(m) \rangle, V[\hat{I}_c(m)]), \quad (12)$$

where $\langle \hat{I}_c(m) \rangle$ is given by (4) and $V[\hat{I}_c(m)]$ by (11).

2.1.2. Approximation with gamma distribution (GD1)

Goebel et al. [18] approximate the expression of distribution for CMI by means of a second order Taylor series expansion. The second order Taylor approximation of MI about $p(x, y) \equiv p(x)p(y)$ (assuming independence) is

$$I(X, Y) = \frac{1}{2 \ln 2} \sum_{x \in X} \sum_{y \in Y} \frac{(p(x, y) - p(x)p(y))^2}{p(x)p(y)},$$

and the estimate $\hat{I}(X, Y)$ is defined accordingly substituting $p(x, y)$ with the observed probability $q_{ij} = n_{ij}/N$, where $i, j \in \{1, \dots, K\}$, and the same for the marginal probabilities. The expression for MI is related to the χ^2 statistic of the standard chi-square test of independence, which is defined as

$$\chi^2 = \sum_{i=1}^K \sum_{j=1}^K \frac{(n_{ij} - (n_{.j}n_{i.})/N)^2}{(n_{.j}n_{i.})/N},$$

and follows a chi-square distribution with $(K - 1)(K - 1)$ degrees of freedom under the assumption of independence of X and Y . The above equations are related by $\chi^2 = 2N \ln 2 \hat{I}(X, Y)$, from which the approximate gamma distribution $\Gamma((K - 1)^2/2, 1/(N \ln 2))$ of $\hat{I}(X, Y)$ is established [18]. Further, it follows that $\hat{I}(X, Y|Z)$ is approximately gamma distributed (denoted hereafter GD1)

$$\hat{I}_c(m) = \hat{I}(X, Y|Z) \sim \Gamma\left(\frac{K_Z}{2}(K - 1)(K - 1), \frac{1}{N \ln 2}\right). \quad (13)$$

2.1.3. Approximation with gamma distribution and moments from normal distribution (GD2)

It is known that a gamma distribution $\Gamma(\alpha, \beta)$ with shape parameter α being a positive integer and scale parameter β , can be approximated by a normal distribution $N(\alpha\beta, \alpha\beta^2)$ if α is sufficiently large [28, 29]. Reversing this result, using the mean and variance of $\hat{I}(X, Y|Z)$ in (4) and (11), respectively, we can estimate the parameters of gamma distribution and obtain approximately the gamma distribution for $\hat{I}(X, Y|Z)$ (denoted hereafter GD2)

$$\hat{I}_c(m) = \hat{I}(X, Y|Z) \sim \Gamma\left(\frac{\hat{I}_c^2}{V[\hat{I}_c]}, \frac{V[\hat{I}_c]}{\hat{I}_c}\right). \quad (14)$$

2.1.4. Parametric tests for the significance of CMI

Having determined the three parametric approximations for the distribution of $\hat{I}_c(m)$, we use them as null distributions for the null hypothesis $H_0: I_c(m) = 0$. Given that it always holds $I_c(m) \geq 0$, all three parametric tests are one-sided. We compute the p -value from the cumulative function of the null distributions ND, GD1 and GD2 of the observed CMI $\hat{I}_c(m)$, and we reject H_0 if the p -value is less than the nominal significance level α (we set $\alpha = 0.05$ for all simulations below). We apply the significance test for increasing orders m until we obtain rejection of H_0 for m and no rejection of H_0 for $m + 1$, and then the estimate of L is m . The parametric tests are denoted as ND, GD1 and GD2 corresponding to the respective null distributions.

2.2. Randomization test for the significance of CMI(RD)

In a recent work [12], we developed a randomization significance test for $I_c(m) = 0$ and formed the null distribution for $H_0: I_c(m) = 0$, empirically. For the randomization test, we first generate M randomized symbol sequences $\{x_t^{*1}\}_{t=1}^N, \dots, \{x_t^{*M}\}_{t=1}^N$ by random permutation of the initial sequence $\{x_t\}_{t=1}^N$. Then we compute $\hat{I}_c(m)$ on the original symbol sequence, denoted $\hat{I}_c^0(m)$, and on the M randomized sequences, denoted $\hat{I}_c^{*1}(m), \dots, \hat{I}_c^{*M}(m)$. Finally, we reject H_0 if $\hat{I}_c^0(m)$ is at the right tail of the empirical null distribution formed by $\hat{I}_c^{*1}(m), \dots, \hat{I}_c^{*M}(m)$. To assess this we use rank ordering, where r^0 is the rank of $\hat{I}_c^0(m)$ in the ordered list of the $M + 1$ values, assuming ascending order. The p -value of the one-sided test is $1 - (r^0 - 0.326)/(M + 1 + 0.348)$ using the correction in [30]. The randomization test is denoted as RD.

2.3. Parametric and randomization significance test for CMI

Here, we show the differences of the distributions ND, GD1 and GD2 in approximating CMI with an example of two Markov chains of order $L = 3$ and $L = 6$, number of symbols $K = 2$ and symbol sequence length $N = 1600$ and $N = 256000$. The true distribution of CMI, $\hat{I}_c(m)$, for order $m = L$, is approximated by 1000 Monte Carlo realizations, as shown in Figure 1 **with the broken line displaying the histogram**. The three approximating distributions are drawn setting their parameters as defined in (12), (13) and (14) to the corresponding average values from the 1000 realizations. As shown in Figure 1, all three approximations match quite well the true distribution of CMI for $L = 3$ (see Figure 1a), but for $L = 6$ ND and GD2 lie to the left while GD1 tends to lie to the right of the true distribution (see Figure 1b). It seems that as the chain order increases, **the approximations of ND, GD1 and GD2 tend to deviate more from the true distribution**. The match tends to be regained by increasing the chain length. Indeed when we increase the sequence length to $N = 256000$, all distributions translate closer to zero and have smaller width, as expected, and the distributions of ND and GD2 approximate better the true distribution, whereas the distribution of GD1 is still at the left of the true distribution (see Figure 1c). The latter indicates that the significance test with GD1 is more conservative, and for this case the probability of rejection of H_0 is expected to be smaller than the nominal significance level.

The three parametric tests are then compared to the randomization test. For one realization of the same Markov chains with $L = 3$ and $L = 6$ ($N = 1600$), the three parametric null distributions and the null distribution formed by CMI values from 1000 surrogates are shown in Figure 2. For $L = 3$ in Figure 2a, the H_0 of $I_c(L) = 0$ is not rejected for any of the one-sided tests with the statistic \hat{I}_c because all four distributions cover well the observed value of $\hat{I}_c(L)$ (shown by a vertical dashed line in Figure 2). On the contrary, for $L = 6$, $\hat{I}_c(L)$ lies towards the right tail of ND and GD2 distribution tending to give false rejection, and on the left of the RD and GD1 distributions giving correctly no rejection (see Figure 2b). Moreover, the null distribution of GD1 is further to the right of the observed value $\hat{I}_c(L)$ than the null distribution of RD, suggesting that the test with GD1 may be more conservative than with RD for this setting.

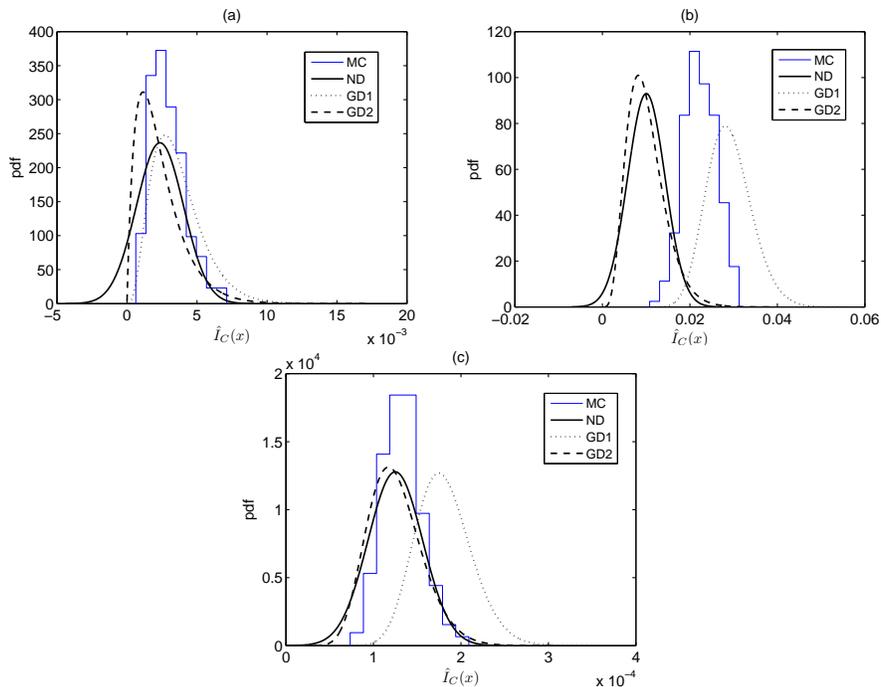


Figure 1: The true distribution of $\hat{I}_C(L)$ and the three approximations ND, GD1 and GD2, formed from 1000 Monte Carlo realizations of a Markov chain of $K = 2$. (a) $L = 3$ and $N = 1600$, (b) $L = 6$ and $N = 1600$, and (c) $L = 6$ and $N = 256000$.

3. Monte Carlo Simulations

We evaluate the three parametric tests (ND, GD1 and GD2) and the randomization test (RD) using Monte Carlo simulations for varying Markov chain order L , number of symbols K and symbol sequence length N . We also compare the RD and parametric tests with four known criteria for the estimation of L : the Akaike's information criterion (AIC) [3, 5], the Bayesian information criterion (BIC) [5], the criterion of Dalevi and Dubashi which is based on the Peres and Shields estimator (PS) [6, 7] and the criterion of Menéndez et al. (Sf) [31, 8]. For each parameter setting, we use 100 realizations, and $M = 1000$ randomized sequences for each realization for the randomization test. The Markov chain order is sought in the range $m = 1, \dots, L + 1$ by applying each of the four significance tests of $I_c(m)$ for increasing order m , as well as the aforementioned criteria. In the first simulation setup, Markov chains are derived by randomly selected transition probability matrices of given order L , while in the second simulation setup, Markov chains are derived by transition matrices of given order L estimated on two DNA sequences of genes and intergenic regions.

3.1. Randomly selected transition probabilities

For each selection of L and K , a symbol sequence of length N is generated from a transition probability matrix of size $K^L \times K$ with randomly selected components from

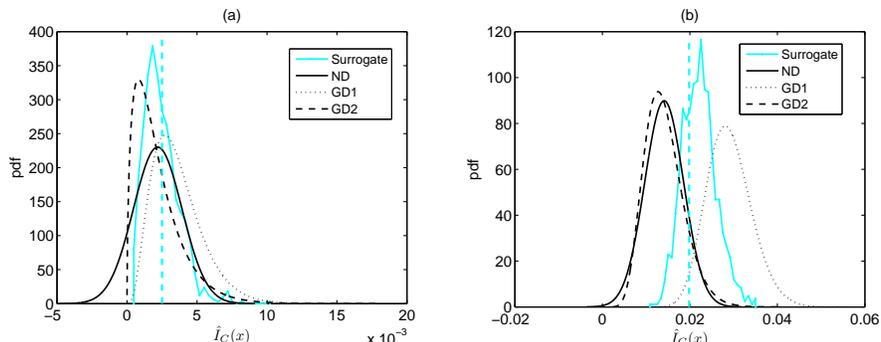


Figure 2: The three parametric approximations of the null distribution of $\hat{I}_c(L)$ and the distribution formed by $M = 1000$ surrogates for one realization of length $N = 1600$, $K = 2$, and (a) $L = 3$, (b) $L = 6$. The observed value of $\hat{I}_c(L)$ is shown by a vertical dashed line.

the uniform distribution $[0, 1]$ under the restriction that the rows of the matrix sum to one. In a pilot study we considered both the setting of selecting a different transition probability matrix for each of the 100 realizations and the setting of using the same transition probability matrix for all realizations with different initial conditions. The results were qualitatively the same and we chose to proceed with the first setting.

As expected, the simulations suggest that for all methods the success rate in identifying the true order L increases with N and decreases with L and K . As shown in Figure 3 for $K = 2$, all criteria attain about the same success rate in detecting the correct L for $L = 2, 3$. **When $N \geq 1600$, the success rate increases with N being close to 100% (see Figure 3e and f). We can also notice that the success rate decreases with L for any N and for all methods, but it decreases differently across the methods. For each N and as L increases, the success rate of GD1, RD and PS decreases slower with L than for the other criteria, with the success rate of PS tending to stay positive even for $L = 10$, e.g. see Figure 3c for $N = 400$.** It is worth noting that GD1 follows well with RD for all N and L and at cases it even scores higher, e.g. for $N = 200$ (Figure 3b) GD1 and RD have a success rate at about 40% for $L = 5$, while for $L = 6$ the success rate decreases slightly for GD1 but dramatically for RD (the success rate of GD1 drops to zero for $L = 7$). In the same example, the success rate for PS decreases smoothly with L . For larger N the three best criteria tend to align, and thus we can safely conclude that these methods perform similarly and distinctly better than the other order estimation criteria. While all criteria improve with N , Sf tends to score low even for small L .

The estimation of L is more data demanding as the number of symbols increases, as shown in Figure 4 for $K = 4$. The success rate tends to increase with N , but for ND, GD2, AIC and BIC this can be seen only for small $L = 2, 3$ (Figure 4a and b), while for larger $L = 4, 5$ (Figure 4c and d) even for the largest examined sequence length $N = 6400$ the success rate is zero. The three best criteria for $K = 2$ perform also best for $K = 4$ with Sf following close for small L and scoring lower as L increases. Here, GD1 and RD have very similar performance, with GD1 scoring more often higher, and they both score highest in most cases, especially for large L and N .

3.2. Transition probabilities estimated on DNA

DNA consists basically of four nucleotides, the two purines, adenine (A) and guanine (G), and the two pyrimidines, cytosine (C) and thymine (T), so a DNA sequence can be considered as a symbol sequence on the symbols A,C,G,T. In our analysis we use a large segment of the Chromosome 1 of the plant *Arabidopsis thaliana*¹. We use two sequences, one sequence derived by joining together the genes, which contain non-coding regions, called introns, in between the coding regions, called exons, and another sequence joining together the intergenic regions which have solely non-coding character. The sequences used here are segments of the long sequences used in [32].

In this simulation setup we form the Markov chains from transition probabilities matrices of given order L estimated on the two DNA sequences of genes and intergenic regions, and we generate 100 symbol sequences from each of these Markov chains for different initial conditions. The purpose here is to consider Markov chains of distinct structure of the probability transition matrix for each order L that relate to a real world Markov chain. The results for the success rate of correct estimation of the true order L with all the criteria and for $K = 2$ (purine and pyrimidine) and $K = 4$ (all four nucleotides), where we set $L = 2, 3, 4, 5$ and N varying from 100 to 6400, are shown in Figure 5 for the genes and in Figure 6 for the intergenic regions. For both genes and intergenic regions, all the criteria fail when the order gets large ($L > 3$) and only PS maintains a positive success rate but at the same low level of 10% - 20% and rather independently of N . For smaller orders ($L = 2, 3$), all criteria tend to improve with N but at low levels of success rate differing across the criteria (for $L = 2$ see Figure 5a and b for genes and $K = 2$ and $K = 4$, respectively, and the same in Figure 6a and b for intergenic regions). These results suggest that the task of estimating the true L of a Markov chain with the structure of transition probabilities as in DNA sequences is more difficult than when the transition probabilities are selected at random. Concerning the CMI-based tests, again ND and GD2 fail to estimate the true L for both genes and intergenic regions, while GD1 follows tightly with RD, both being suboptimal but scoring consistently well compared to all other criteria. For example for genes and $L = 2$, when $K = 2$ (Figure 5a) GD1 and RD score lower than PS and AIC for all N (and higher than all others), but when $K = 4$ (Figure 5b) GD1 and RD score higher than AIC for all N and PS at large N . AIC scores highest of all criteria for $K = 2$ but it has zero success rate when $K = 4$, and only for $L = 2$ the success rate increases above zero with large N (Figure 5b), indicating that the data requirement for AIC with the increase of K is disproportionately high compared to the other criteria. On the other hand, PS estimates correctly the order L at the same low rate regardless of N for $L > 3$, being however higher than for other criteria. This somehow peculiar performance of PS is explained by the fact that for $L > 3$ PS estimates at random the order L , so that it hits the true order at a percentage of cases dependent on the range of the tested m values, whereas the other criteria underestimate the order. GD1 and RD have thus the most consistent behavior, increasing the probability (success rate) to identify the true order with N at a level depending on L and K .

Comparing the results of the criteria for the two types of DNA sequences, they

¹Data were obtained from the database: <http://www.ncbi.nlm.nih.gov>

match pretty well for the corresponding K , L and N . Though the relative differences of the criteria are the same, the level of success rate tends to be higher for the intergenic regions, specifically for $K = 2$, indicating that the Markov chain of the same order L obtained on the basis of intergenic regions is less complex, i.e. the order is better detectable than for the genes. For example, for $K = 2$ and $L = 3$, it can be seen in Figure 5c that GD1 and RD reach a success rate of 40% at the largest tested $N = 6400$ for genes, while for the intergenic regions the corresponding success rate is at 60% (Figure 6c). The overall results show that when the transition probabilities are estimated on DNA sequences of genes and intergenic regions, all the criteria fail for larger orders, having somehow higher success rates for intergenic regions.

4. Application on DNA sequences

Much of the statistical analysis of DNA sequences is focused on the estimation of properties of coding and non-coding regions as well as on the discrimination of these regions. There has been evidence that there is a different structure in coding and non-coding sequences and that the non-coding sequences tend to have long range correlation, whereas the correlation in coding sequences exhibits exponential decay [33, 34, 35]. Here we use intergenic and gene sequences. The latter is a mixture of coding regions (exons) and non-coding regions (introns), and therefore we expect to have also long range correlation due to the non-coding regions in it, but it should be less than the correlation in the intergenic regions consisting only of non-coding parts. Thus both DNA sequences cannot be considered as Markov chains, at least not of a moderate order, and the estimation of the order L should increase with the available data size.

We estimate the order L of a hypothesized Markov Chain underlying Chromosome 1 of plant *Arabidopsis thaliana* by the three parametric tests ND, GD1 and GD2, the RD, as well as the criteria of AIC, BIC, PS and Sf. The computations are done for both genes and intergenic regions of length $N = 8000, 16000, 32000, 64000$ and 128000 and for $K = 2$ (purines, pyrimidines). As shown in Figure 7, the order estimated by any of the four criteria based on CMI, and for both genes and intergenic regions, increases with the length N of the DNA sequence, indicating the presence of a Markov chain of a very large order (larger than the maximum order that can be detected for this N) or a chain with long range correlations. The limits of detectable order for $N = 8000$ (Figure 7a) are $L = 4$ for intergenic regions, obtained by GD1, RD and AIC, and $L = 6$ for genes, obtained by AIC whereas all four CMI-based criteria estimate $L = 1$. The largest estimations of L increase for $N = 16000$ to $L = 8$ and $L = 4$ for intergenic regions and genes, respectively (Figure 7b). The criterion of Sf gives about the same pattern of increasing estimated order with N and larger estimate of L for intergenic regions than for genes. On the other hand, the estimated L from the criteria AIC, BIC and PS changes irregularly with N and is not always larger for the intergenic regions, giving inconclusive results. The agreement of L estimation by GD1 and RD is remarkable, both giving exactly the same estimate for any of the two DNA types and for any but the largest length $N = 128000$. For $N = 128000$ (Figure 7e), the difference is small for genes with GD1 estimating $L = 11$ and RD $L = 10$, and larger for intergenic regions with GD1 giving $L = 16$ and RD $L = 11$. The other two CMI

based criteria, ND and GD2, give estimates of L close to these of GD1 and RD, and so does Sf but tending to give somewhat smaller estimate of L as N increases. The overall results suggest that the symbol sequence of intergenic regions tend to have larger order and thus being more consistent to the hypothesis of long range correlation. This is confirmed by the four CMI based criteria and Sf, but RD and GD1 in addition turn out to be able to estimate large L , as justified also by the simulation results.

5. Conclusions

In this work we propose and assess parametric tests of significance of the conditional mutual information (CMI) for the estimation of the order of Markov chain. The null distribution of CMI is approximated by the normal distribution and two different approximations of gamma distribution. Simulations showed that among the three parametric tests the one based on gamma distribution (GD1) performed best for any Markov chain order L and number of symbols K and even for short lengths of symbol sequences. The practical aim of the study was to investigate whether a parametric test can reach the order estimation accuracy of the respective randomization test (RD), recently implemented and found to be compatible and often better than the known order estimation criteria. The simulation study confirmed that GD1 performs similarly to RD and both compare favorably to other known criteria (AIC, BIC, the Peres and Shields estimator and the criterion of Menéndez et al. [31, 8]).

Having established the equivalence of performance of GD1 and RD, the advantage of GD1 is the computational efficiency, allowing the order estimation based on CMI to be possible for very long symbol sequences, such as the DNA sequences. Obviously, RD applied with a number M of randomized sequences (in this work we used $M = 1000$) requires about M times more computation time than GD1, and thus application of RD is prohibitive for very long symbol sequences. This was the case of DNA sequences, and for $N = 128000$, RD was running on a PC Intel Core CPU 2, 83GHz 3, 5GB RAM for about 2 days.

Using the parametric and randomization tests, as well as the Sf criterion on purine and pyrimidine sequences of genes and intergenic regions from the Chromosome 1 of plant *Arabidopsis thaliana*, we could establish an increase of the estimated order with the length of the DNA sequence, indicating the presence of either a very large Markov chain order not reached by the tested sequence lengths or long range correlations (this is further explored in a focused study in [19]). Further, we could also distinguish genes from intergenic regions as lower order was estimated in genes, which consists of coding and non-coding parts, than in intergenic regions which contains non-coding parts exclusively.

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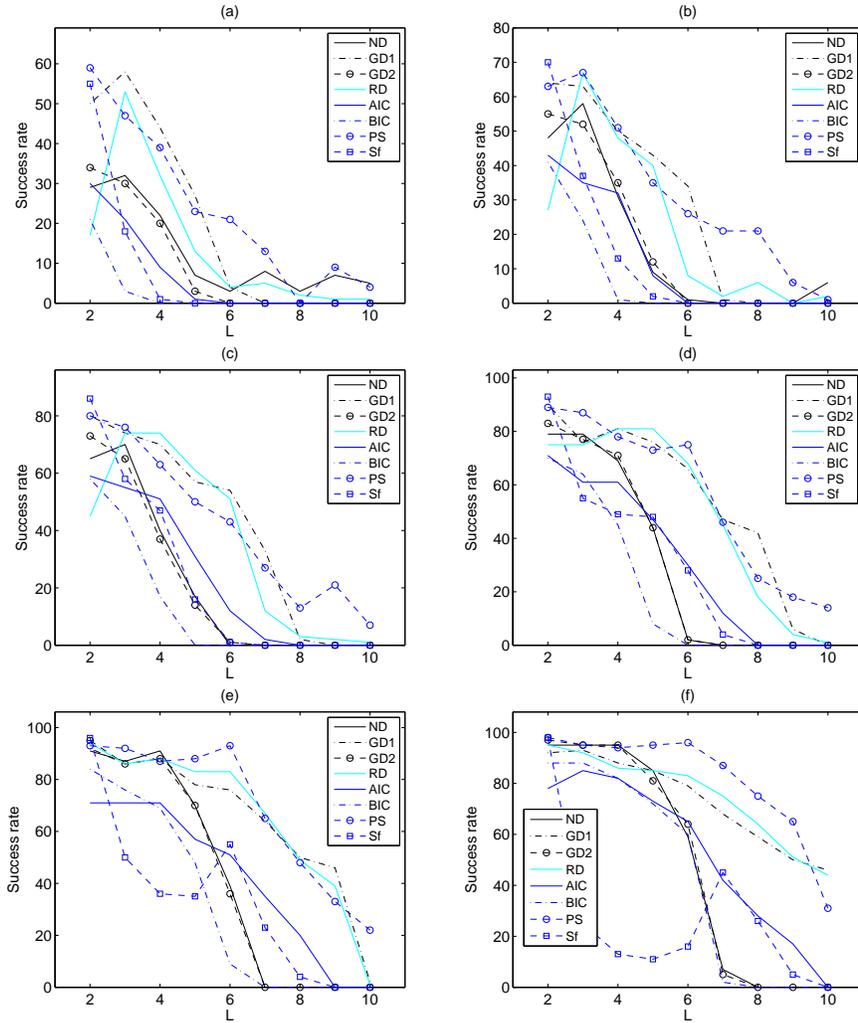


Figure 3: Number of cases out of 100 realizations the true order L is estimated by the criteria ND, GD1, GD2, RD, AIC, BIC, PS and Sf vs order L , as shown in the legend. The symbol sequences have length (a) $N = 100$, (b) $N = 200$, (c) $N = 400$, (d) $N = 800$, (e) $N=1600$ (f) $N=3200$, and they are generated by a Markov chain of $K = 2$ symbols with a randomly selected transition probability matrix.

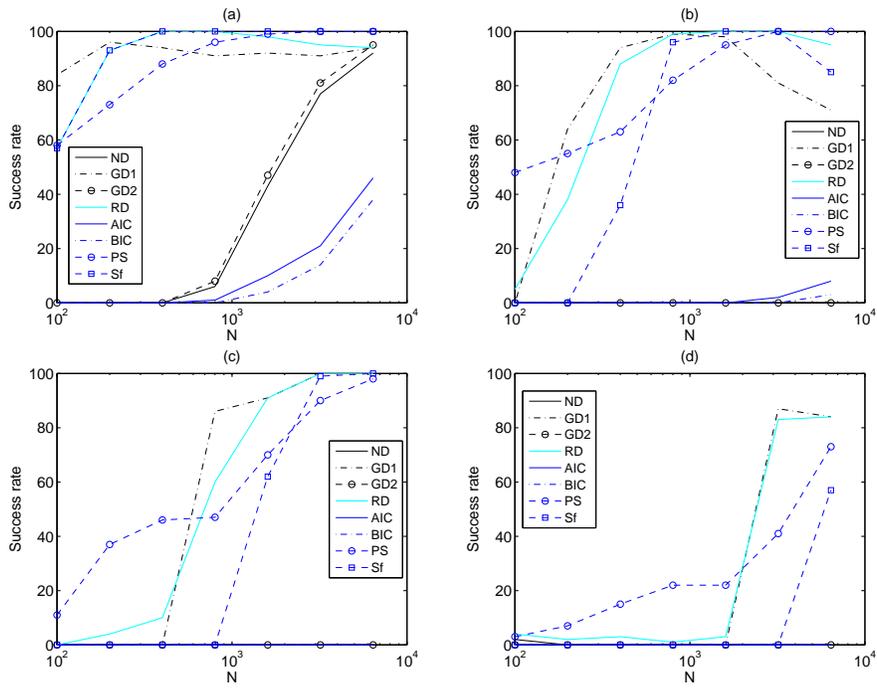


Figure 4: Number of cases out of 100 realizations the true order L is estimated by the criteria ND, GD1, GD2, RD, AIC, BIC, PS and Sf vs sequence length N , as shown in the legend. The symbol sequences are generated by Markov chains of $K = 4$ symbols with a randomly selected transition probability matrix and order (a) $L = 2$, (b) $L = 3$, (c) $L = 4$ and (d) $L = 5$.

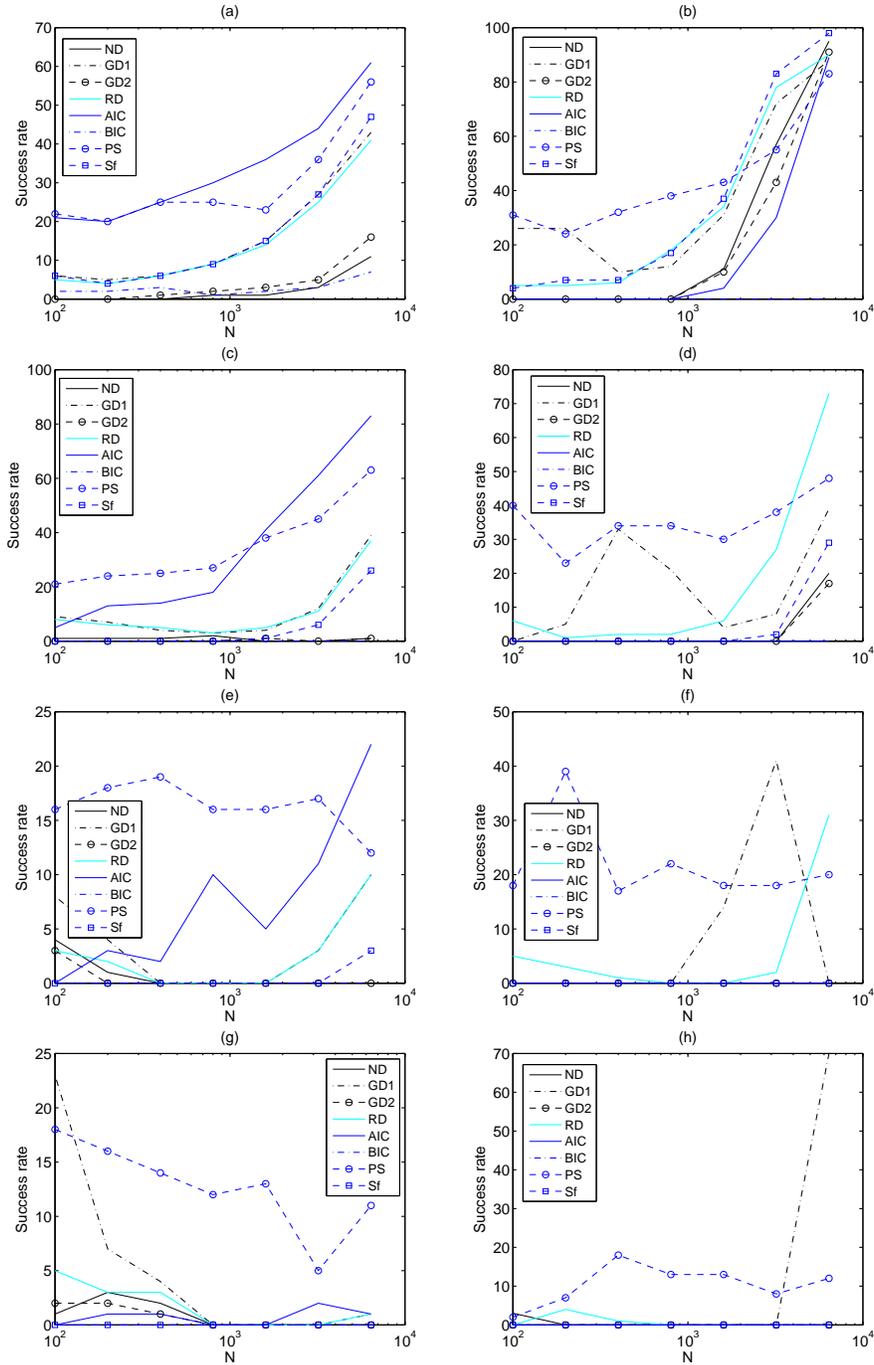


Figure 5: Number of cases out of 100 realizations the true order L is estimated by the criteria as shown in the legend, vs sequence length N . The symbol sequences are generated by Markov chains of transition probability matrices estimated on a DNA sequence of genes. The panels are for purines and pyrimidines ($K = 2$) and $L = 2, 3, 4, 5$ in (a), (c), (e), (g), respectively, and for the four nucleotides ($K = 4$) and $L = 2, 3, 4, 5$ in panels (b), (d), (f), (h), respectively.

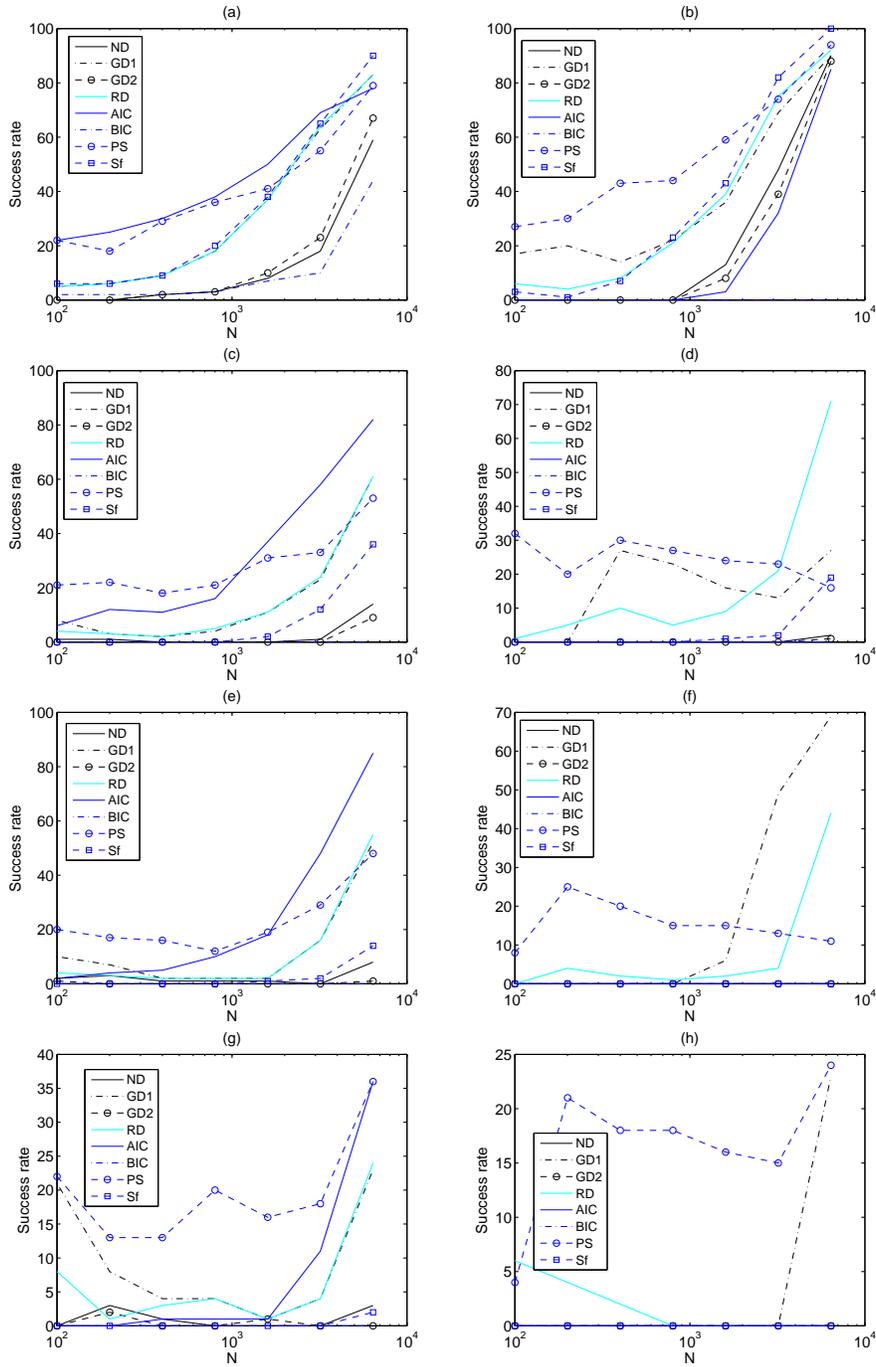


Figure 6: (a) Same as for Figure 5, but for the DNA sequence of intergenic regions.

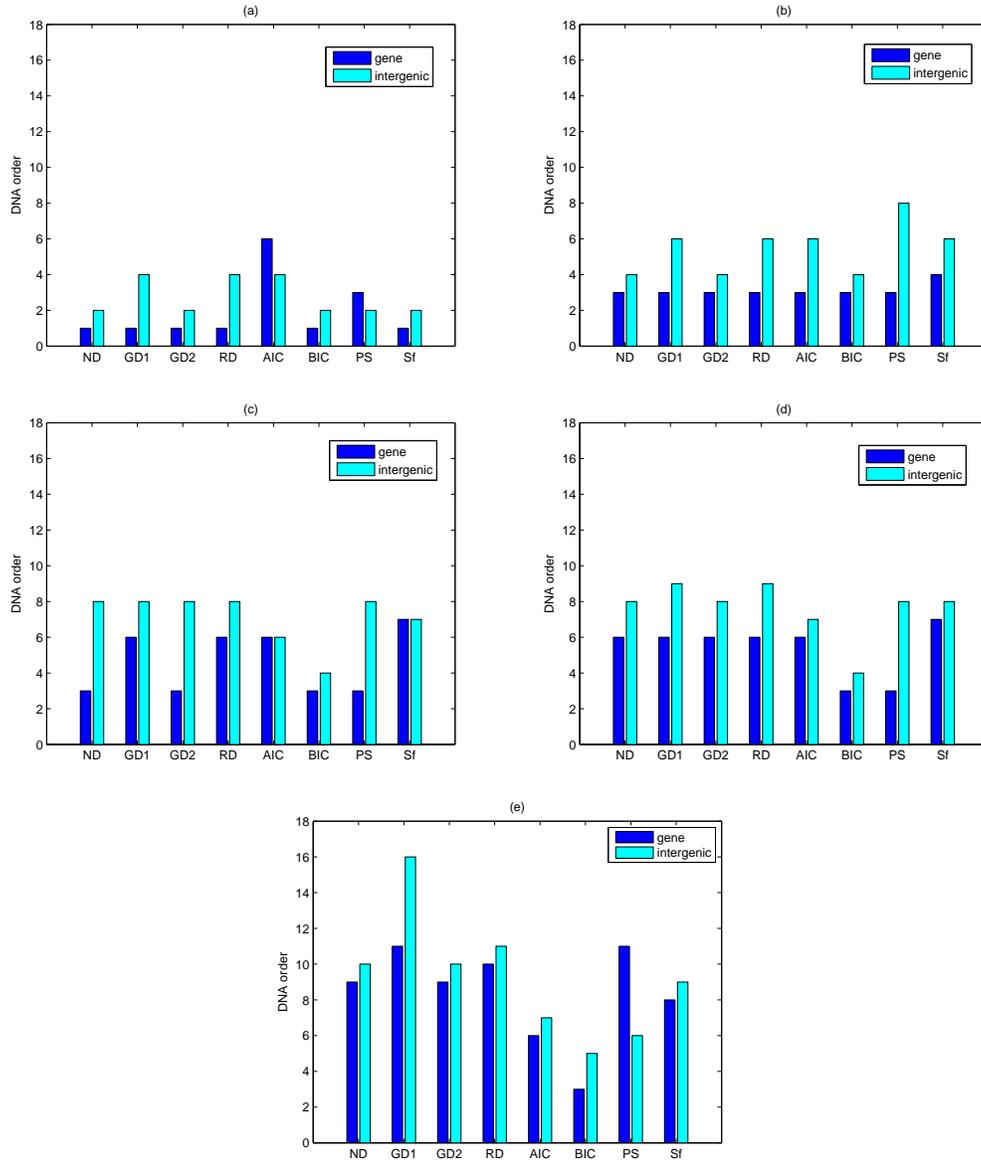


Figure 7: The estimated order L by ND, GD1, GD2, RD, AIC, BIC, PS and Sf of sequences of purine and pyrimidine ($K = 2$) from genes and intergenic regions of Chromosome 1 of the plant *Arabidopsis thaliana*, as indicated in the legend. The sequence lengths are (a) $N = 8000$, (b) $N = 16000$, (c) $N = 32000$, (d) $N = 64000$ and (e) $N = 128000$.