LOCALIZING TIME-VARYING PERIODICITIES IN SYMBOLIC SEQUENCES

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ABSTRACT

A novel approach is presented to the detection of time-varying periodicities in symbolic sequences. Various symbolic sequences like DNA can be modelled as stochastic processes that exhibit time-varying cyclostationarity. The coding part of the DNA, for instance, exhibits statistical periodicity with period three. The complexity-regularized maximum-likelihood estimates are developed in this paper for the statistical period of symbolic sequences. The time-varying periodicities are discovered by using sliding windows. A cumulative sum test is also presented to detect the change points. The formulation in this paper avoids any kind of numerical mapping for the symbolic DNA sequences and does not impose any algebraic structure.

Index Terms— Symbolic periodicity, finding exons, cyclostationarity.

I. INTRODUCTION

SYMBOLIC sequences are time series defined on a finite set with no algebra. In DNA sequences, economic indicator data, and other nominal time series, the only mathematical structure is the set membership [1]. An interesting and important behaviour such symbolic sequences may exhibit is *periodicity* and finding such periodicities is fundamental to the understanding and determination of the structure of the sequences. In genomic signal processing, locating hidden periodicities in DNA sequences is important since repetitions in DNA have been shown to be correlated with several structural and functional roles [2]. For example, a base (symbol) periodicity of 21 is associated with α-helical formation for synthesized protein molecules [2] and a base periodicity of 3 is identified with exons, the protein coding region of the DNA. Such investigations also find applications in diagnosis of genetic disorders (like Huntington's disease [3]), DNA forensics and reconstructing evolution history [4].

Symbolic periodicities can be classified into homologous, eroded, and latent Homologous periodicities occur when short fragments are repeated in tandem. Eroded periodicities [5] result when some of the symbols in a homologous periodic sequence are replaced or altered so that the tandem repeats are imperfect. These may also be observed as *indels* (insertions and deletions) in homologous periodic sequences. Latent periodicities [5] occur when the repeating unit is not a fixed sequence but may change in a patterned way: for instance, a sequence in which the nth element is always either A or G. An observed latent period of nucleotides in a DNA sequence may be (A/C)(T/G)(T/A)(G/T)(C/G/A)(G/A), i.e. the first nucleotide of a period may be A or C followed by a T or G and so on.

Symbolic random variables take values on a set called the *alphabet* whose elements are called *symbols*. A symbolic sequence is defined as a sequence of symbolic random variables. Most current approaches to detecting periodicities transform the symbolic sequences into a numerical sequence [6].which defines an algebra on the alphabet. But this imposes a mathematical structure that is not present in the problem. For instance, the mapping of DNA elements (T$=0$, C$=1$, A$=2$, G$=3$), suggested in [7], puts a total order on the set; the complex representation (A$=1+j$, G$=-1+j$, C$=-1-j$, T$=1-j$) used in [8], [6] implies that the euclidean distance between A and C is greater than the distance between A and T. A good survey of various numerical representations for DNA sequences is presented in [9]. Most of these techniques are primarily aimed at the detection of homological periodicities [10], [8], [11]. Artifacts of such mappings are reported in [11].

In contrast, the formulation in this paper implies no mathematical structure on the alphabet and presents a general approach to the detection of the three classes of periodicities in a maximum likelihood framework. Each symbol of the sequence is assumed to be generated by an information source with some underlying probability mass function(pmf). The sequence is generated by drawing symbols from these sources in a cyclic manner. Thus, periodicities in the symbols are represented by repetitions of the pmfs, referred to as *statistical periodicity* or *strict sense cyclostationarity*. The number of sources is equal to the latent period in the sequence.

The problem of detecting latent periodicities in symbolic sequences is formulated mathematically in the next section. The maximum likelihood estimate of the period were developed in [12]. The estimates are improved in this paper by incorporating a complexity term with the likelihood

function in section III. This penalized maximum likelihood estimator is justified by the application of the minimum description length (MDL) principle to the model selection problem. In section IV the MDL estimates are computed in sliding windows over various simulated and real DNA sequences. The series of estimates characterizes the time-varying behaviour of the sequences.

II. STATISTICAL PERIODICITY

A given symbolic sequence $D = D_1 D_2 \ldots$ can be denoted by the mapping $D : \mathbb{N} \rightarrow \mathcal{X}$, from the natural numbers to an alphabet $\mathcal{X}$. For DNA sequences, $\mathcal{X} = \{\mathrm{A}, \mathrm{G}, \mathrm{C}, \mathrm{T}\}$ where the symbols denote nucleotides Adenine, Guanine, Thymine and Cytosine respectively. Let P denote a probability distribution on $\mathcal{X}$ and X denote the corresponding random variable or information source. Let $\mathcal{X}^n$ denote the n-fold cartesian product of $\mathcal{X}$ and $x^n \in \mathcal{X}^n$ denote a random sequence of length n. A *probabilistic source* is defined as a sequence of probability distributions $P^{(1)}, P^{(2)}, \ldots$ on corresponding sequence of alphabets $\mathcal{X}^1, \mathcal{X}^2, \ldots$ such that for all n, and for all $x^n \in \mathcal{X}^n$, $P^{(n)}(x^n) = \sum_{y \in \mathcal{X}} P^{(n+1)}(x^n, y)$.

If a symbolic sequence D is generated by repeatedly picking subsequences from a probabilistic source $P^{(\mathcal{T})}$ and concatenating them, then the statistical periodicity of D is $\mathcal{T}$. In other words, the sequence D is generated by $\mathcal{T}$ information sources denoted as $X_1, \ldots, X_{\mathcal{T}}$, in a cyclic fashion. The random variable X_i takes values on the alphabet $\mathcal{X}$ according to an associated probability mass function P_i; it generates the j^{th} symbol in $\mathcal{X}$ with probability $P_i(j) = \mathcal{P}(X_i = \mathcal{X}_j)$ for $j = 1, \ldots, |\mathcal{X}|$ where $|\mathcal{X}|$ is the cardinality of the alphabet (which is four for the DNA sequences).

The number of complete statistical periods in D are $M = \lfloor N/\mathcal{T} \rfloor$, where $\lfloor x \rfloor$ denotes the largest integer that is smaller than or equal to x. Define $\widehat{i}_{\mathcal{T}} = 1 + ((i-1) \mod \mathcal{T})$, where $(x \mod y)$ denotes the remainder after division of x by y. Then for $1 \leq i \leq N$, the symbol D_i, i.e. the i^{th} symbol in the sequence D, is generated by the random variable $X_{\widehat{i}_{\mathcal{T}}}$. The random variables $X_{\widehat{i}_{\mathcal{T}}}$ for $\widehat{i}_{\mathcal{T}} = 1, \ldots, \mathcal{T}$ are assumed to be independent. The *parameters*, $P_1, \ldots, P_{\mathcal{T}}$, and $\mathcal{T}$ are unknown. Define $\Theta = [\mathcal{T}, P_1, \ldots, P_{\mathcal{T}}]$. The search space for parameter $\mathcal{T}$ is the set $B = \{1, \ldots, N_0\}$, for some $N_0 < N$ and for the pmfs $\mathbf{Q} = [P_1, \ldots, \mathcal{P}_{\mathcal{T}}]$ the search space is the subset $\mathcal{Q} \subseteq [0,1]^{|\mathcal{X}| \times \mathcal{T}}$ of column stochastic matrices (for $\mathbf{Q} \in \mathcal{Q}$, $\mathbf{Q}_{ji} \in [0,1]$ and $\sum_{j=1}^{|\mathcal{X}|} \mathbf{Q}_{ji} = 1$ for $i = 1, \ldots, \mathcal{T}$). Let $\wp = B \times \mathcal{Q}$ denote the search space for the parameter Θ. Given the data, the maximum aposteriori (MAP) estimate of parameter Θ is

$$\Theta_{\text{MAP}} = \arg\max_{\Theta \in \wp} \mathcal{P}(\Theta|D) = \arg\max_{\Theta \in \wp} \mathcal{P}(D|\Theta)\mathcal{P}(\Theta), \quad (1)$$

using the Bayes rule and the fact that $\mathcal{P}(D) = \int_{-\infty}^{\infty} \mathcal{P}(D|\Theta)\mathcal{P}(\Theta) d\Theta$ is a constant. Under the uniform prior assumption the estimates for the unknown parameters were presented in [12]. However, as seen from the experimental results on simulated sequences and real gene data, the estimates tend to overfit the data. To address the problem of over-fitting, a penalized maximum likelihood estmator is suggested in section III. The estimator is derived using the refined minimum description length (MDL) principle. The penalization then corresponds to assuming the universal prior on the parameters and refined MDL estimator is essentially the MAP estimator with respect to the universal prior.

III. PENALIZED MAXIMUM LIKELIHOOD ESTIMATOR

The fundamental idea or the intuition behind MDL is that more regular the data is, the easier it is to compress and thus learn [13]. Let D denote the data and let $\mathcal{H}^{(1)}, \mathcal{H}^{(2)}, \ldots$ be a list of candidate models or hypotheses, where $\mathcal{H}^{(k)} = \{Q | Q \text{ is an } M \times k \text{ column-stochastic matrix}\}$ for $k = 1, \ldots, N_0$. Define $\mathcal{H} = \cup_{k=1}^{N_0} \mathcal{H}^{(k)}$. Then the best explanation of the data D is the hypothesis $H \in \mathcal{H}$ that minimizes the description length

$$L(D|\mathcal{H}) = L(\mathcal{H}^{(k)}) + L(D|\mathbf{Q}_{\text{ML}}^{(k)}) \quad (2)$$

where $L(\mathcal{H}^{(k)})$ is the length, in bits, of the description of the hypothesis $\mathcal{H}^{(k)}$ and $L(D|\mathbf{Q}_{\text{ML}}^{(k)})$ is the length, in bits, of the description of the data when encoded by the best maximum likelihood hypothesis $\mathbf{Q}_{\text{ML}}^{(k)} \in \mathcal{H}^{(k)}$. The term $L(D|\mathcal{H})$ is sometimes referred to as the *stochastic complexity* of the data given the model whereas $L(\mathcal{H}^{(k)})$ is called the *parametric complexity*. Clearly, the MDL model selection involves the trade-off between goodness-of-fit and complexity.

The second term $L(D|\mathbf{Q}_{\text{ML}}^{(k)})$ in the two part code, represents the codelength of the data when encoded with the hypothesis $\mathbf{Q}_{\text{ML}}^{(k)}$. Assuming the hypotheses are probabilistic, the Shannon-Fano code is optimal in terms of the expected codelength. Thus, $L(D|\mathbf{Q}_{\text{ML}}^{(k)}) = -\log P(D|\mathbf{Q}_{\text{ML}}^{(k)})$, where $P(D|\mathbf{Q}_{\text{ML}}^{(k)})$ is the probability of observing D conditioned on the hypothesis $L(D|\mathbf{Q}_{\text{ML}}^{(k)})$. The codelength is therefore the negative-log-likelihood of having observed the data D. As presented in [12], the $(j, \widehat{i}_k)^{th}$ element of the matrix $\mathbf{Q}_{\text{ML}}^{k}$ is given as

$$\mathbf{Q}_{\text{ML}}^{k}(j, \widehat{i}_k) = \frac{1}{M} \sum_{m=1}^{M} \mathbf{1}\{D_{(m-1)k+\widehat{i}_k} = \mathcal{X}_j\}, \ \widehat{i}_k = 1, \ldots, k \quad (3)$$

where $\mathbf{1}\{\cdot\}$ is the indicator function. The MLE for the probability mass functions of the random variables is intuitive. Simply stated, given the period k, segment the data sequence in non-overlapping contiguous subsequences of length k. The pmf of the m^{th} information source is given by the relative frequencies of each symbol. So, for instance, if the hypothesized statistical period in a gene sequence is 3 then

the MLE of the pmf of the 2^{nd} information source is given by the relative frequencies of nucleotides in the subsequence comprises of every third symbol, starting with the second.

For the first term in equation (2), the following code may be adopted. First encode k using $\lceil \log k \rceil$ $1'$s followed by a 0 which is followed by another $\lceil \log k \rceil$ bits for the binary representation of k. Note that this a prefix code and takes $2\lceil \log k \rceil + 1$ bits. The parameters of $Q \in \mathcal{H}^{(k)}$ are described by $k' = Mk$ frequencies or probabilities that are determined by the counts in the set $\{0, 1, \ldots, \lceil \frac{N}{k} \rceil\}$, thus taking $k' \log(\lceil \frac{N}{k} \rceil + 1)$ bits. The total codelength for the code is therefore

$$L(H)+L(D|H) = 2\lceil \log k \rceil + 1 + Mk \log \lceil \frac{N}{k} \rceil - \log P(D|H) \tag{4}$$

for $H \in \mathcal{H}^{(k)}$. Its clear from the equation above that the MDL principle yields a penalized maximum likelihood estimate. The code used here is a *universal code* and implies a universal prior on the hypothesis.

IV. TIME VARYING PERIODICITIES

The penalized MLE is applied to various simulated symbolic sequences and real gene sequences. In order to detect time-varying periodicities in a sequence of N symbols, the estimates are computed in a sliding window of size $M < N$ with an overlap of H symbols between successive windows. Figure 1 shows results for a simulated 8000-symbols long DNA sequence that has latent periodicity of period 6 for subsequences with indices $1-2000$ and $6001-8000$ and is completely random in the middle. Thus there are two *change points* in the sequence. The latent period of the periodic part of the sequence is (A/C)(T/G)(T/A)(G/T)(C/G/A)(G/A), i.e. it was generated by six information sources, $X_1, \ldots, X_6$ with X_1 generating A or C each with equal probability, X_5 generating A,G or C each with probability $1/3$ and so on. The window size was chosen to be 750 symbols and the overlap was 675 symbols. The description length (Z-axis) is plotted for the ML hypothesis corresponding to each period (Y-axis) along the sequence (X-axis). Note that both change points are detected in the surface plot. Also the six-periodic behaviour is very evident from the plot as are the harmonics, i.e. the integer multiples of the true period.

The algorithm was also tested with chromosome 20 of the human genome [14]. The 9748 base-pair(bp) long sequence (from bp 22,553,000-22,562,747) contains 1305 long (bp 22,557,488-22,558,792) protein coding region (*exon*) flanked by non-coding parts (*introns*) on both sides. The contour plot in Figure 2 shows a latent periodicity of period three beginning at sliding window number 60 which corresponds to bp number 22,557,427 ($M = 750$, $H = 75$). The period-3 behaviour of protein coding genes is expected since amino acids are coded by trinucleotide units called *codons* [6].

The window size M determines the usual trade-off between the resolution and the accuracy of the estimates. The larger the window size, the better the estimates since the averaging in the empirical estimator is over more data. On the other hand, smaller windows give better resolution since the estimates along the sequence depend only on the input symbols in a small neighbourhood. Another problem with poor resolution is detecting two change points that are very close to each other. For instance, if the random part of the sequence in figure 1 is much smaller than the window size, the change points may go undetected. A multi-resolution multi-scale technique is therefore preferred where various sizes for the sliding window are used. A coarse search is first performed followed by a fine search in the regions of interest.

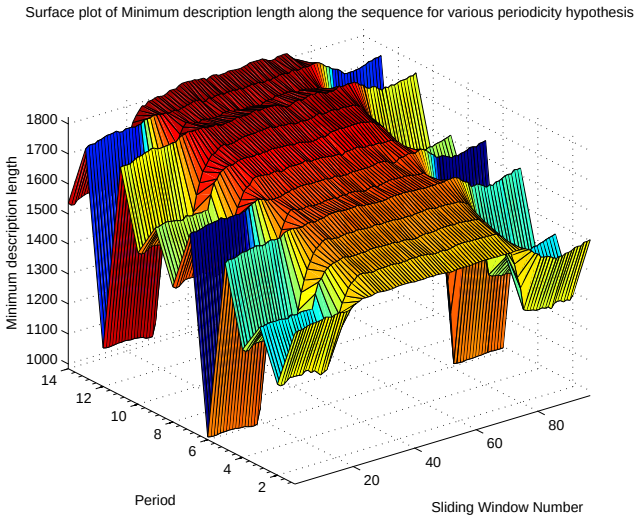

Fig. 1. Description length (in bits) for the ML estimate in $\mathcal{H}^{(k)}$ plotted against period k along the sequence.

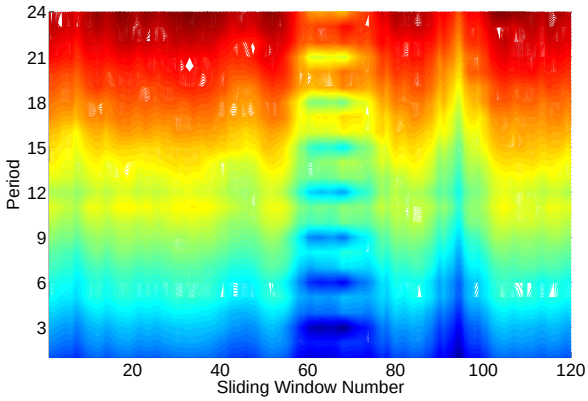

Fig. 2. Contour plot of description length (in bits) for the ML estimate in $\mathcal{H}^{(k)}$ plotted against period k along the sequence.

Near the change points, the periodicity profile gradually changes, whereas in other parts the profile remains constant except for some small fluctuations due to the noisy data. Thus a uniformly most powerful (UMP) test may be constructed based on the positive inflection rate over multiple successive windows. If the maximum likelihood period reported is P then the alternate composite hypothesis is that the period is no longer P. The formulation is very similar to the change-point problem in statistics. The test proposed here is similar to the cumulative sum approaches. The null hypothesis that there is no change is rejected if

$$\mathbf{\Theta}_t^{(P)} = \min_{m\in\{1,\ldots,T\}} |\mathbf{Q}_{\mathrm{ML},t}^{(P)} - \mathbf{Q}_{\mathrm{ML},t-m}^{(P)}|_{\mathrm{tot}} > \delta_{\mathrm{Th}} \quad (5)$$

where $|\mathbf{A}-\mathbf{B}|_{\mathrm{tot}} = \sum_{i,j}(a_{ij}-b_{ij})^2$ is the total deviation between matrices $\mathbf{A}$ and $\mathbf{B}$, δ_{Th} is a threshold and T is the number of successive windows over which the test is conducted. The test statistic $\mathbf{\Theta}_t^{(P)}$ for period P is the minimum total deviation between ML estimates for the pmfs in window t and previous T windows. $\mathbf{\Theta}_t^{(P)}$ is plotted in figure 3 for the simulated latent periodic sequence used in figure 1. The jump in $\mathbf{\Theta}_t^{(6)}$ at $t=9$ corresponds to the change-point at bp number $M+8\times H = 1950$, giving much better resolution. The resolution can be further improved upon by decreasing H, keeping M constant. Note that $\mathbf{\Theta}_t^{(6)}$ is consistently large over the transition regions with lobe-width equal to M.

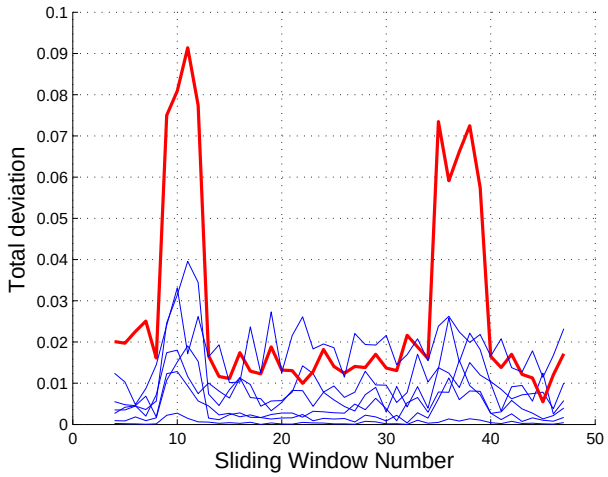

Fig. 3. $\mathbf{\Theta}_t^{(P)}$ plotted along the sliding window number for the sequence from figure 1. $\mathbf{\Theta}_t^{(6)}$ is plotted in red. ($M = 750, H = 150, T = 3$)

V. DISCUSSION

The various parts of DNA sequences exhibit characteristic statistical periodicities. Mapping this behaviour to structural and functional roles is an important aspect of genomic signal processing. The investigation is challenging at least in part due to the lack of an algebraic structure. The approach used here models the symbolic sequence as a nonstationary random process on a finite alphabet. The time-varying nature of symbolic sequences is studied and a uniformly most powerful test is constructed for detecting the transition points.

VI. REFERENCES

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