DNA Segmentation as A Model Selection Process

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ABSTRACT
Previous divide-and-conquer segmentation analyses of DNA sequences do not provide a satisfactory stopping criterion for the recursion. This paper proposes that segmentation be considered as a model selection process. Using the tools in model selection, a limit for the stopping criterion on the relaxed end can be determined. The Bayesian information criterion, in particular, provides a much more stringent stopping criterion than what is currently used. Such a stringent criterion can be used to delineate larger DNA domains. A relationship between the stopping criterion and the average domain size is empirically determined, which may aid in the determination of isochore borders.

1. INTRODUCTION
A typical DNA sequence is not homogeneous. There are local regions with contrast: C+G rich versus C+G poor; protein-coding regions with a strong signal of periodicity-three versus non-coding regions lacking this periodicity; high densities of 5’-CG-3’ dinucleotides (CpG island) versus low density of this dinucleotide; etc. Finding the exact border between these regions is an important task in DNA sequence analysis. It is a common practice to use a moving window to visually monitor the variation of the quantity of interest (e.g. C+G density) along the sequence, and the border is determined in an ad hoc way. With the sequence information, it is actually possible to determine the border exactly by certain mathematical criterion.

These mathematical approaches to delineate regional homogeneous domains are known as “segmentation” [2], “partitioning”, or “change-point analysis” [1, 3, 4] in different fields ranging from image processing to statistics. There are segmentation methods that require guessing the number of homogeneous regions. There are also segmentation methods that require specification of the number of types of domains (e.g. C+G rich and C+G poor represent two types of domains, whereas C+G high, intermediate, and low specify three types). Segmentation analysis of DNA sequences can be found in [8, 15, 33].

One particularly attractive segmentation method is a divide-and-conquer approach [4, 28] (similar recursion processes are also discussed in statistics and machine learning under the names of “classification and regression tree” [10], “recursive partitioning” [18], “decision tree induction” [26, 31], etc). The DNA sequence is first segmented into two subsequences so that base compositions on two sides of the partition are maximized. Then, the same procedure is carried out on both the left and the right subsequences; and then on the sub-subsequences, etc. Eventually, either the size of a subsequence is too small to segment, or the difference between the left and right subsequences is not big enough to be worth further segmentation. Recursive segmentation offers the following advantages: there is no need to specify the number of homogeneous domains beforehand; the number of types of domains need not to be specified (it is implied in the stopping criterion); there is no constraint on the size distribution of the domains (such a constraint exists in hidden-Markov-model-based segmentations); and the computation is efficient.

This paper addresses one of the disadvantages of this segmentation: the stopping criterion of the recursion. Another disadvantage of this approach – the fact that the solution is a local maximum with no guarantee of the global maximum being obtained – is not addressed here. In principle, one can set any stopping criterion, leading to domains of any sizes. In the hypothesis testing framework of statistics, whether a test is “significant” or not (corresponding to a continuation, or a termination, of the recursion in our case) is decided by a pre-set “significance level”. Usually, the significance level can be 0.05, 0.01, or 0.001. These levels are arbitrary and will not guarantee objectivity [3].

We provide a stopping criterion based on the framework of model selection (for a detailed discussion of the hypothesis testing framework versus the model selection framework, see [4]). This new stopping criterion offers at a minimum condition for the recursive segmentation to continue. On the other hand, in the hypothesis testing framework, no such minimum condition exists; for example, the 0.06 significance level is weaker than the 0.05 level, and 0.1 is even weaker than 0.06, etc. In the model selection framework, there are
two different guiding principles. The first is to choose a model that most closely approximates the true model. The second is to find the true model among a list of candidate models. The first principle leads to a technique of Akaike Information Criterion (AIC), and the second leads to the technique of Bayesian Information Criterion (BIC). We will show that BIC-based stopping criterion for segmentation is practically more useful.

2. METHODS

2.1 The divide-and-conquer segmentation in its original formulation

The original publication of this divide-and-conquer segmentation method is called “entropic segmentation” [23,24], because the quantities used in determining the partition point are based on entropy, a statistical physics concept. The entropy of a sequence with length \( N \) and number of bases \( \{N_\alpha\} (\alpha = a, c, g, t) \) is calculated as (‘‘means that the quantity is estimated from the data)

\[
\hat{E}(\{N_\alpha\}) = \sum_{\alpha=a,c,g,t} \frac{N_\alpha}{N} \log \frac{N_\alpha}{N} \tag{1}
\]

Given a partition point \( i \) (\( 1 < i < N \)), an entropy-based quantity called Jensen-Shannon distance (divergence) [25] is defined as

\[
\hat{D}_{JS} = \hat{E}(\{N_\alpha\}) - \frac{i}{N} \hat{E}(\{N_{\alpha,l}\}) - \frac{N-i}{N} \hat{E}(\{N_{\alpha,r}\}) \tag{2}
\]

where \( \{N_{\alpha,l}\} \) and \( \{N_{\alpha,r}\} \) are the base counts of the left (from position 1 to \( i \)) and the right (from position \( i+1 \) to position \( N \)) subsequences (with \( \sum_\alpha N_{\alpha,l} = i, \sum_\alpha N_{\alpha,r} = N - i \)). The partition point \( i \) is chosen to maximize \( \hat{D}_{JS} \).

2.2 The divide-and-conquer segmentation as a likelihood ratio test

In fact, the above entropic description can be cast into a hypothesis testing framework – the likelihood ratio test [26]. Likelihood is simply the probability of observing the data, given a model, with emphasis on the functional dependence on the model parameter (in other words, the normalization coefficient is not needed). To test whether a model is “significant”, the likelihood under the model (\( L_2 \)) is calculated, and maximized over all possible parameters (\( L_2 \)). A similar calculation is carried out on the null model (\( L_1 \) and \( \hat{L}_1 \)). If the null model is the correct model of the data, and if the null model is nested in the alternative model, it can be shown that in the large sample size limit [27]

\[
2 \log \frac{L_2}{L_1} \sim \chi^2_{df=K_2-K_1} \tag{3}
\]

where \( \chi^2_{df} \) is the chi-squared distribution with degrees of freedom \( df \) (i.e. sum of \( df \) terms of squared unit normal distribution), \( K_2 \) and \( K_1 \) are the number of free parameters in maximizing \( L_2 \) and \( L_1 \).

In our divide-and-conquer segmentation, \( L_1 \) is the likelihood assuming the sequence being a random sequence, and \( L_2 \) is the likelihood assuming two random subsequences:

\[
L_1(\{p_\alpha\}) = \prod_\alpha p_\alpha^{N_\alpha},
\]

\[
L_2(\{p_{\alpha,i}\}, \{p_{\alpha,r}\}, i) = \prod_\alpha p_{\alpha,l}^{N_{\alpha,l,i}} \prod_\alpha p_{\alpha,r}^{N_{\alpha,r,i}} \tag{4}
\]

where \( \{p_\alpha\} (\alpha = a, c, g, t) \) is the base composition of the whole sequence (here these are free parameters in the model to be estimated), \( \{p_{\alpha,l}\} \) and \( \{p_{\alpha,r}\} \) are the same base compositions of the left and right subsequences. The maximum likelihood estimation of a base composition is simply the percentage of the base: \( p_\alpha = N_\alpha / N \). It can easily be shown that \( 2 \log (L_2/L_1) \) is the same as \( 2N \hat{D}_{JS} \). The number of parameters in the two models are \( K_2 = 7 \) (the partition point \( i \) is also a free parameter) and \( K_1 = 3 \). So \( 2N \hat{D}_{JS} \) under the null hypothesis should obey the \( \chi^2_{df=4} \) distribution (the same conclusion was reached before, see [6] and ([Grosse, et al. in preparation], only the \( df \) used there is 3, instead 4).

2.3 The divide-and-conquer segmentation as a model selection

There are many shortcomings in the hypothesis testing framework [28]. The purpose of a test is to see how bad a description of the data \( L_1 \) is, not how good a description \( L_2 \) is. For many circumstances, it is not really what we are interested in. In the model selection framework, we directly address the “merit” of a model. One measure of such a “merit” is whether the model is close (a better approximation) to the true model. The closeness is measured by the Kullback-Leibler distance (divergence) [20], and the Akaike Information Criterion (AIC) is one approximation of this distance (with the constant term removed, and multiplied by a factor of 2) [24]:

\[
AIC = -2 \log (\hat{L}) + 2K + O\left(\frac{1}{N}\right), \tag{5}
\]

where \( \hat{L} \) is the maximized likelihood of the model, \( K \) is the number of free parameters in the model. A model with the lowest AIC is closest to the true model, thus the best approximating model.

Another “merit” of a model is how the data increases the probability of the model (only in Bayesian statistics is it possible to extend the concept of probability to the model and its parameters). The factor between the prior and posterior probability of the model is the “integrated likelihood” [22]. An asymptotic approximation of minus-twice the logarithm of the integrated likelihood is the Bayesian Information Criterion (BIC) [24]:

\[
BIC = -2 \log (\hat{L}) + \log (N)K + O(1) + O\left(\frac{1}{\sqrt{N}}\right) + O\left(\frac{1}{N}\right), \tag{6}
\]

where \( N \) is the sample size. A model with the lowest BIC has the largest integrated likelihood, and this translates to the largest posterior probability if all models have the same prior probability. Note that AIC emphasizes an approximation of the true model, and BIC emphasizes the selection of the true model from the space of all models. The high-order terms in AIC are discussed in [37, 19], and the derivation of BIC can be found in [32]. It can easily be seen that if \( \log (N) > 2 \) (or
\( N > 7.389 \), the penalty on the number of model parameters (i.e. the second term in Eq.(6) and Eq.(1)) in BIC is more severe than that in AIC. As a result, BIC tends to select simpler models than AIC.

When the segmentation is viewed as a model selection process, the model before the segmentation describes the sequence as a random sequence, whereas that after the segmentation describes it as two random subsequences. Since AIC/BIC must decrease for the segmentation to continue, it can be shown that they lead to the two stopping criteria as follows:

\[
\begin{align*}
\text{AIC-based stopping criterion} & : 2N\hat{D}_{JS} > 8 + O\left(\frac{1}{N}\right) \\
\text{BIC-based stopping criterion} & : 2N\hat{D}_{JS} > 4\log(N) + O(1) + O\left(\frac{1}{\sqrt{N}}\right) + O\left(\frac{1}{N}\right).
\end{align*}
\]

It is interesting to compare these criteria with those in the hypothesis testing framework. Setting the value of \( \chi^2_{df=4} \), the corresponding significance level (p-value, tail-area) is 0.091578. In the hypothesis testing framework, it is allowed to set an even more relaxed significance level such as 0.1, but in the AIC-based model selection, 0.091578 is the limit of allowed levels. Similarly, with a given sequence length \( N \), the limit of allowed levels can be determined by a BIC-based model selection; for example, if \( N = 1\text{Mb} \), the significance level is 2.8631 \times 10^{-11}. Again, the significance level can not be more relaxed than these limits.

Besides limits on the relaxed side of the stopping criterion, there are no theoretical limits on the stringent side. One model can be “marginally better” than another model, “moderately better”, or “much better”, etc. We will show that one can gradually make the stopping criterion more stringent so that average domain size is increased. For convenience, we define the “strength” of a 1-to-2 segmentation as the percentage increase of \( 2N\hat{D}_{JS} \) over the BIC-defined stopping threshold:

\[
\text{strength} = \frac{2N\hat{D}_{JS} - 4\log(N)}{4\log(N)}.
\]

The strength has to be larger than 0, but it has no upper limit.

### 3. RESULTS

Since the AIC-based stopping criterion is more relaxed than the typical 0.01-significance-level test, one will end up with more domains than from the program discussed in [28]. The BIC-based stopping criterion, however, is more interesting for our purpose, because it provides a theoretical justification for using a much more stringent stopping criterion than those typically used in the hypothesis testing framework. We illustrate the BIC-based segmentation by three DNA sequences with a wide range of sequence lengths.

#### 3.1 Lambda phage

Fig.1 shows the result for \( \lambda \) bacteriophage (\( N = 48,502 \) b) [35]. This sequence has been tested with various segmentation methods in [28]. There are several pieces of information displayed in Fig.1: the domain borders obtained by the BIC-based segmentation on the original four-symbol sequence (upper bars); the borders segmented by the two-symbol (CG vs. AT) sequence (middle bars); the borders obtained by the AIC-based segmentations (with higher-order terms included) (dots; due to the limitation of resolution, individual dots can be hard to see); a moving-window C+G content along the sequence; the strength of the segmentations as defined in Eq.(8) (lower spikes); and the sequential order of early-rounds of segmentations (e.g. the first partition point from the 1-to-2 segmentation is labeled “1st”). We note the following: (1) Segmentation results from the four-symbol sequence and the two-symbol sequence are different. (2) The number of domains by segmenting the four-symbol sequence is 6, which is the same as results from a two-state hidden Markov segmentation as discussed in [3]. The BIC-based stopping criterion, however, is more interesting for our purpose, because it provides a theoretical justification for using a much more stringent stopping criterion than those typically used in the hypothesis testing framework. We illustrate the BIC-based segmentation by three DNA sequences with a wide range of sequence lengths.

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Figure 2: Human major histocompatibility complex (MHC) sequence.
eters (in contrast to tuning of the significance level in the hypothesis testing framework), the BIC-based segmentation manages to obtain a reasonable number of domains (AIC-based segmentation, on the other hand, leads to too many domains).

### 3.2 MHC

Fig. 2 shows the result for the human major histocompatibility complex (MHC) sequence \( (N = 3,673,778 \text{ b}) \). The MHC sequence is a highly gene-rich region (with more than 200 genes) that is located on the short-arm of chromosome 6 of the human genome. The segmentation result captures the complexity of this sequence. With so many domain borders in Fig.2, we only show those that have strengths larger than 100%. Historically, the MHC sequence is divided into three domains (in the telomere-to-centromere direction): class-I, class-III (C+G-rich), class-II (C+G-poor). The MHC sequencing project added another C+G-rich domain to the end: extended-class-II. Interestingly, the border of these domains can be easily detected by segmentation (these results are from the two-symbol segmentation): I/III: \( i = 1,841,871, \text{ strength} = 23679.6\% \), III/II: \( i = 2,483,966, \text{ strength} = 17084.7\% \), II/extended-II: \( i = 3,384,907, \text{ strength} = 28849\% \). These three 1-to-2 segmentations are the strongest. With this segmentation result, the domain sizes of class I, III, II, and extended-II are: 1.84 Mb, 0.64 Mb, 0.90 Mb and 0.29 Mb. The number of segmented domains in the MHC sequence is very large (1260 from the BIC-based two-symbol segmentation and 1828 from the BIC-based four-symbol segmentation). Segmentation with the minimum requirement (i.e. for BIC to decrease) not only leads to large, 100kb-plus domains, but also leads to smaller-scaled base composition fluctuation. This “domains-within-domains” phenomenon has been discussed in [25, 4, 22, 23]. If one is only interested in isochores, i.e., large DNA segments with usually 300 kb or longer that have relatively homogeneous base composition [25], a more stringent criterion has to be used (to be discussed later).

### 3.3 Left-arm of Drosophila chromosome 2

The last sequence to be segmented is the left arm of Drosophila melanogaster chromosome 2 \( (N = 22,075,671 \text{ b}) \). There is 1.78% of the sequence that is not determined (symbol “n” or “N”). To preserve the location information, these undetermined symbols are replaced randomly by the four nucleotides (according to the actual base composition of this sequence). Only the 1-to-2 segmentations with strength larger than 200% are included in Fig.3, and only the result for the four-symbol sequence is displayed. The segmentation of a four-symbol sequence is more likely to cut the telomere (as well as centromere) at an earlier stage than the corresponding two-symbol sequence; and this is shown in Fig.3. This observation can be used to delineate complex sequence patterns in telomere sequences (D Kessler and W Li, in preparation).

Although the drosophila sequence is much longer than the MHC sequence, there is only one 1-to-2 segmentation of the drosophila’s left-arm of chromosome 2 that has a similar strength as those of the MHC sequence leading to domain borders. This occurs at position 6,959,803 with the strength 16768%. If we use a similar strength criterion as that used in delineating three domain classes in the MHC sequence, there is only one domain border in this sequence.

### 3.4 How stringent the stopping criterion has to be to reach a certain domain size

Since the model selection framework only provides a limit on the relaxed end of the stopping criterion, the stringent end is in principle open. Nevertheless, we can empirically determine the typical domain size as a function of the stringency of the stopping criterion. Fig.4 shows the average domain sizes versus the threshold value for the strength, all based on the four-symbol segmentation. Besides the three sequences used in Figs.1-3, results from Escherichia coli \( (N = 4,639,221 \text{ b}) \), the right arm of Drosophila melanogaster chromosome 2 \( (N = 20,228,487 \text{ b}) \), and yeast Saccharomyces cerevisiae chromosome 3 \( (N = 315,341 \text{ b}) \) are also included.
Fig. 4: Average domain size vs. threshold for segmentation strength.

Plots like Fig. 4 are similar to the “compositional complexity” [34, 23, 5]. The difference is that in [34, 23, 5], not only the number of domains, but also the base composition difference between domains is part of the measure of complexity. In Fig. 4, it is purely the number of domains. Nevertheless, the plot of Fig. 4 is useful because it provides practical guidance on the choice of stopping criterion at the stringent end. This choice will subjectively depend on what length scales are of interest to the investigator.

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