SEGMENTATION AND ESTIMATION OF CHANGE-POINT MODELS

XIAO FANG, JIAN LI AND DAVID SIEGMUND

The Chinese University of Hong Kong, Adobe Systems and Stanford University

Abstract

To segment a sequence of independent random variables at an unknown number of change-points, we introduce new procedures that are based on thresholding the likelihood ratio statistic. We also study confidence regions based on the likelihood ratio statistic for the change points and joint confidence regions for the change-points and the parameter values. Applications to segment an array CGH analysis of the BT474 cell line are discussed.

AMS 2000 subject classification: 62G05, 62G15.

Keywords and phrases: Array CGH analysis, change-points, confidence regions, exponential families, likelihood ratio statistics.

1 Introduction

Diverse scientific applications have led to recent interest in segmentation of models involving multiple change-points. A model having some direct applicability and additional theoretical interest for the insights it provides is as follows. Let $X_1, X_2, \ldots, X_m$ be independent and normally distributed with variances equal to 1. Assume that there exist $M \geq 0$ and integers $0 = \tau_0 < \tau_1 < \ldots < \tau_M < \tau_{M+1} = m$ such that the mean $\mu_i$ of $X_i$ is a step function with constant values on each of the intervals $(\tau_{i-1}, \tau_i]$, but different values on adjacent intervals. Segmentation amounts to determining the value of $M$, the $\tau_i$ and perhaps also the $\mu_i$. Because of the computational difficulty of sorting through all possible partitions of $[1, m]$ to find the change-points when $m$ is large, there have often been different algorithms for suggesting a set of candidate change-points $\tau_i$ and for determining which of those possible sets is “correct.” For example, one might use a dynamic programming algorithm to propose a relatively small set of possible $M$ and $\tau_i, 1 \leq i \leq M$, then use a statistical procedure to determine a final choice from those suggested in the first stage of analysis. For recent reviews imbedded in otherwise original research articles see Frick, Munk and Sieling (2014).

1
and Fryzlewicz (2014). Another recent paper that provides motivation for our research is Niu and Zhang (2012), who also emphasize tentative selection of several sets of candidate change-points followed by model selection to make the final choice. The procedures suggested below could also form part of a two-stage procedure, but here we consider in detail only a single stage, which allows us to obtain control of the rate of false positives.

Substantial motivation for recent research has been copy number variation (CNV) in genetics (e.g., Olshen et al. (2004), Pollack et al. (1999), Picard et al. (2004), Lai et al. (2005), Snijders et al. (2003), Zhao et al. (2004), Zhang and Siegmund (2007), Niu and Zhang (2012), Frick, Munk and Sieling (2014), Zhang et al. (2016)). CNV can occur as somatic mutations, especially in cancer cells, where they can involve a substantial portion of a chromosome and show no particular pattern, or as germline mutation, which like other genetic polymorphisms can be used to track relatedness in populations or may be of interest because of their possible relation to particular inherited diseases. Data in the literature can help us determine interesting sample sizes and values for parameters in our numerical examples. The sample size $m$ is typically large, while $M$ can be small or large in an absolute sense, while still small compared to $m$; and consecutive change-points can be very close together. Another genomic application involves sequences of Bernoulli variables, which equal 0 or 1 according as the DNA letter at that location is A or T, or is C or G. Since a CG “rich” region is an indication of the presence of a gene or genes, it may be useful to segment a genome or part of a genome into regions of relatively low or high CG content. See, for example, Churchill (1989) who used a Hidden Markov Model, or Elhaik, Graur, and Josić (2010).

A variety of other examples motivated by particular scientific experiments is given by Du, Kao and Kou (2016). In particular they describe examples where several consecutive changes are expected to have the same sign and where the pattern of change-points appears may arise from a hidden Markov model. Recent consistency results under essentially minimal conditions on the spacing and amplitude of the change-points are given in Chan and Chen (2017).

In the frameworks described above, scientific focus emphasizes detection and estimation of the change-points, estimation of the step function of mean values, or a combination of the two. Like the classical problem of online detection of a change-point that indicates appearance of a fault in a production process, our primary focus is on the change-points themselves, which in a genomic context indicate the existence and location of a signal of interest.

To this end we study iterative thresholding methods that allow one (with varying degrees of success, discussed below) to control the global false positive error rate; and subject to successful control, to understand the relative strengths and weaknesses of different methods. We also provide approximations to the local power (defined below) and large sample joint confidence
regions for the change-points or for the change-points and mean values.

To motivate the methods introduced below let \( S_j = \sum_{i=1}^j X_i \) and consider the generalized likelihood ratio statistic for testing the hypothesis \( M = 0 \) against \( M = 1: \max_j |S_j - jSm/m|/(j(1 - j/m))^{1/2} \). This statistic is the basis of the binary segmentation suggestion of Vostrikova (1981), which is a “top down” procedure, in the sense that one tests all the data to determine if there is at least one change-point and iterates the procedure in the intervals immediately to the “left” and “right” of the most recently detected change-point. How one should choose a threshold at each stage is unclear. For a given threshold, the false positive probability for this statistic is sub-additive in \( m \), so use of the same threshold at each iteration can lead to an uncontrolled false positive rate when the number of changes is large.

Instead we consider “bottom up” procedures motivated by the observation that in the presence of multiple change-points, it seems appropriate to compare a candidate change-point at \( j \) to an appropriate “local” background \((i, k)\), where \( i < j < k \). To that end, consider \( \max_{i,j,k} |Z_{i,j,k}| \), where for \( i < j < k \):

\[
Z_{i,j,k} = [S_j - S_i - (j-i)(S_k - S_i)/(k-i)]/[(j-i)(1-(j-i)/(k-i))]^{1/2}. \tag{1.1}
\]

Our first theoretical result is an approximation for the tail probability of \((1.1)\) when there is no change. This approximation gives strong control on the probability of a false positive result in the sense that if there are changes, say at \( 0 = \tau_0 < \tau_1 < \ldots < \tau_M < \tau_{M+1} = m \), the maximum of \((1.1)\) over \( n = 0, \ldots, M \) and \( \tau_n \leq i < j < k \leq \tau_{n+1} \) is stochastically smaller than the unrestricted maximum of \((1.1)\). Hence, except for an event of arbitrarily small probability, any background interval \([i, k]\) where the statistic exceeds the threshold at an intermediate value of \( j \) will contain at least one change-point (although it may not be close to the maximizing value of \( j \)).

Our second principal result is approximate likelihood ratio confidence regions jointly for the change-points \( \{\tau_k, k = 1, \ldots, M\} \) or for the change-points and the mean values. A related result allows one to approximate the local power (defined below), which we find useful in helping us understand which change-points are relatively easily detected and which may be missed.

In more detail, our segmentation procedure based on \((1.1)\) is as follows. Because of local correlations between different \( Z_{i,j,k} \), thresholding \((1.1)\) produces a set of candidate change-points \( j \), each potentially having multiple backgrounds \((i, k)\). We require that the background for one candidate change-point \( j \) not overlap another candidate change-point \( j' \) in the sense that if \( j < j' \), the corresponding backgrounds should satisfy \( k \leq j' \) and \( i' \geq j \). This can be accomplished by sequentially re-evaluating candidate change-points until they satisfy the constraint. Hence, when a new change-point is identified, the existing putative change-points to its left and to its right may need to be removed or altered. An approach that requires very
little and usually no re-evaluation of candidate change-points is to select the shortest of the possible backgrounds \((i, k)\) from among those for which \(Z_{i,j,k}\) exceeds the required threshold. If there is a tie for the shortest value of \(k - i\), we choose the one with the largest value of \(|Z_{i,j,k}|\). In the examples given below selection based on the largest value of the statistic rarely leads to significant differences from selection based on the shortest background.

To determine the confidence regions discussed below, we are interested in the size, as well as the location, of the change. In these cases we use the largest \(|Z|\)-value, subject to no overlap. This is typically based on a longer background and hence seems to provide a more accurate estimator of the size of the change. Since we have “paid up front” for protection against false positive errors, we can also choose to look at a number of candidate change-point–background combinations to find one that seems appropriate, perhaps by looking for its consistency with other combinations.

We also study a pseudo-sequential procedure where we initially set \(i = 0\), find the smallest \(k > i + 1\) such that \(\max_{i<j<k}|Z_{i,j,k}|\) is above an appropriate threshold, set \(j_1\) equal to the largest such \(j\) or the maximizing value of \(j\), then set \(i = j_1\) and iterate the process. See the unpublished Stanford Ph. D. thesis of E.S. Venkatraman for an early discussion of a similar idea.

The paper is organized as follows. In Section 2 we give approximations to control the false positive probabilities of our segmentation methods. Approximate joint confidence regions are discussed in Section 3. Using simulations and analysis of some real data, we compare our methods in Section 4 with other thresholding methods that control false positive probabilities with varying degrees of success, while Sections 5-7 contain extensions to exponential families and additional discussion. In Appendices A and B, we prove the theorems stated in Sections 2 and 3. In Appendix C, we give properties of some of the statistics used in Section 4.

Motivation for our approach to segmentation appears in Fryzlewicz (2014), whose “wild binary segmentation” uses a random subset of integers \(i, k\), then compares \(\max_j|Z_{i,j,k}|\) to (apparently) an empirically chosen threshold, and in Niu and Zhang (2012), whose statistic is similar to (1.1), although the background is required to be symmetric about \(j\), and only a limited range of backgrounds is considered.

Remarks. (i) For some applications, e.g., for inherited CNV, the signal to be detected extends over a relatively short range in the form of a departure from a baseline value where one change is followed by a second, nearby change in the opposite direction. For problems of this form it seems reasonable to use statistics adapted to the expected shape of the signals, (e.g., Olshen et al. (2004), Frick. Munk and Sieling (2014), Zhang et al. (2010)). We consider such procedures in Section 4, where we show that they perform very well even when there is no particular pattern to the change-points.
(ii) We have assumed the variance of the observations is known. Since the sequences are usually long, under our assumption of independence the variance can usually be estimated very accurately by one half the average of the squared differences of consecutive observations. This estimator avoids the substantial upwards bias that exists when there are multiple change-points and the changes themselves show no particular pattern. We have used it below in our examples, where in many cases the usual estimator incurs a substantial loss of power. The usual estimator is adequate when the data are of the form envisioned in Remark (i), where change-points occur in a relatively sparse set of departures from a baseline value followed by a return to the baseline a few observations later. Our preferred estimator is clearly inadequate when the data are autocorrelated, a problem we hope to deal with in the future.

(iii) In recent research some authors recommend a multiscale modification of the likelihood ratio statistic, which would modify (1.1) by subtracting, say \( \{2\kappa \log[3m/(j-i)(1-(k-j)/(k-i))]/2\}^{1/2} \), in order to obtain greater power to detect relatively small changes that persist over longer intervals at the cost of less power to detect large changes that come relatively close together. See, for example, Dümbgen and Spokoiny (2001) and Frick, Munk and Sieling (2014). Our methods can be adapted to study these modifications, and in Section 4 we investigate a procedure based on the statistic recommended in Frick, Munk and Sieling (2014). However, for the following reasons, these methods are not central to our studies. (a) For problems of CNV detection, difficult detections in the synthetic data suggested in the literature and in the real data in Section 4 usually involve short intervals. (b) What appear in the data to be small changes often arise from technical artifacts in the data and are not scientifically interesting (cf. Olshen et al. (2004) and Zhang et al. (2010)).

(iv) Our methods apply to multivariate data with some (mostly minor) changes. This case is particularly interesting for detection of inherited CNV, which are short and sometimes difficult to detect in single DNA sequences (e.g., Zhang et al. (2010)). In this case it is also interesting to infer which subsets of the distributions have changed at the various change-points.

2 Approximate \( p \)-values

In what follows we write \( A \asymp B \) to mean that \( 0 < c_1 \leq A/B \leq c_2 < \infty \) for two absolute constants \( c_1 \) and \( c_2 \), and \( A \sim B \) means \( A/B \to 1 \); also \( \varphi \) and \( \Phi \) are the standard normal probability density function and distribution function, respectively.

We have the following \( p \)-value approximation for \( \max_{0 \leq i<j<k \leq m} |Z_{i,j,k}| \).

**Theorem 2.1.** Let \( (X_1, \ldots, X_m) \) be an independent sequence of normally distributed random variables with mean \( \mu \) and variance 1 Then for \( Z_{i,j,k} \) be
defined by (1.1), we have for $b \to \infty$ and $m \times b^2$,

$$\begin{align*}
\mathbb{P}\{ \max_{0 \leq i < j < k \leq m} |Z_{i,j,k}| \geq b \} & \sim \frac{1}{4} b^6 f_1(b^2) \sum_{u,v \in \{1,\ldots,m\} : u+v \leq m} (m-u-v)/uv \nu[b(u+v)/u] \nu[b(u+v)/v] \nu[b(u+v)/(u+v)]^{1/2}, \\
& \text{(2.1)}
\end{align*}$$

where $f_d$ is the $\chi^2$ probability density function with $d$ degrees of freedom. The function $\nu$ is defined, e.g., in [Siegmund and Yakir (2007) p. 112 and given to a simple approximation by the equation

$$\nu(x) = (\Phi(y) - 1/2)/[y(y\Phi(y) + \varphi(y))],$$

where $y = x/2$.

The proof of Theorem 2.1 is deferred to Appendix A. We use a new method beginning from an observation of [Zhang and Liu (2011)], which was used there as the basis for Monte Carlo simulation with a one (time) dimensional random field and which we have used for an analytic approximation involving maxima of certain three (or higher dimensional) random fields. Other methods that appear to be adaptable, albeit with more and less intuitive computation, are those of [Siegmund (1988a) and of Yakir (2013)]. Based on other, similar, calculations (see Appendix C) we conjecture that a version of Theorem 2.1 holds for $d$-dimensional Gaussian vectors $X_j$ orthogonalized by the inverse square root of their covariance matrix.

For a multiscale statistic along the lines suggested in Remark (iii) at the end of Section 1, where we subtract, for example, $\{2\kappa \log[3m(k-i)/(j-i)(k-j)]\}^{1/2}$ from (1.1) a similar approximation holds, with the right hand side modified by replacing $b$ by $b(u,v)+\{2\kappa \log[3m(u+v)/uv]\}^{1/2}$ and moving the expressions involving $b(u,v)$ inside the summation. See (7.16) for a similar approximation involving the [Frick, Munk and Sieling (2014)] recommended statistic.

In applications we may wish to put a lower and an upper bound on the length of the background, e.g., $m_0 \leq j-i, k-j \leq m_1$. The appropriate change to (2.1) is to restrict the summation on the right-hand side to $m_0 \leq u,v \leq m_1$. An alternative constraint on the size of the background, which yields a slightly different approximation, is $k-i \leq m_1$. For applications where very short intervals between change-points can occur, we often want to take $m_0 = 1$. There usually is considerable flexibility in choosing $m_1$. Relatively small values of $m_1$ serve two purposes. They can be used to minimize detection of small jumps, which may themselves reflect experimental artifacts leading to drift in the underlying distributions (cf. Olshen et al. (2004), Zhang et al. (2010)); and they speed up what may otherwise be time consuming computations for large values of $m$. 

6
For the pseudo-online procedure, we have a similar approximation to the probability of a false positive detection.

**Theorem 2.2.** Let \((X_1, \ldots, X_m)\) be an independent sequence of independent standard normal random variables. Let \(Z_{i,j,k}\) be defined as in (1.1). We have for \(b \rightarrow \infty\) and \(m \approx b^2\),

\[
P\{ \max_{0<j<k\leq m} |Z_{0,j,k}| \geq b \} \sim \frac{1}{2} b^3 \varphi(b) \sum_{1<k\leq m} \sum_{0<j<k} j^{-2} \nu[b(((k-j)/(jk))^{1/2}] \nu[b(k/(j(k-j)))^{1/2}].
\]

Compared to the segmentation procedure based on (1.1), the pseudo-sequential procedure has the advantages that it is easier to implement. Its disadvantages are that we do not have as strong a theoretical guarantee that the false positive error probabilities are controlled, and detected change-points may not be as accurately estimated.

The statistic suggested by Niu and Zhang (2012) uses the local maxima with respect to \(j\) of

\[
Z_{j,h} = ||(S_{j+h} - S_j) - (S_j - S_{j-h})||/(2h)^{1/2},
\]

where \(h\) is a parameter to be chosen. This statistic also compares the data at a putative change-point to the local background, which is chosen to be symmetric about the putative change-point. Since there is no obvious choice for \(h\) without prior knowledge of the data, Niu and Zhang suggest maximizing (2.3) over a finite number of values of \(h\). For their applications to copy number variation, they suggest 3 values, 10, 20, and 30.

The methods of proof of (2.1) and (2.2) use the fact that local perturbations of these processes lead to approximately independent random walks. Since the local random walks obtained from perturbations of \(j\) and \(h\) are not independent in the case of (2.3), we cannot apply the same methods. They are weakly positively dependent, so it seems natural to conjecture that treating them as if they were independent would produce a slightly conservative approximation. An approximation to the tail probability of the maximum over \(j\) and \(h\) of (2.3), calculated on the assumption that the local increments obtained from perturbations of \(j\) and \(h\) are independent is given by

\[
P\{ \max_{0<t<m, \ 0<h<\min(t,m-t)} |Z_{t,h}| \geq b \} \sim 1.5mb^3 \varphi(b) \sum_{h} \nu[b(3/h)^{1/2}] \nu[b(1/h)^{1/2}] / h^2.
\]

Because of the restriction to a symmetric background for the Niu-Zhang statistic, it can suffer a serious loss of power when change-points are spaced irregularly, with some being close to others.
Table 1 compares the approximation (2.1) and its variations by constraining $m_0 \leq j - i, k - j \leq m_1$ with simulated values obtained from 2000 repetitions.

Table 1: Approximation (2.1). Simulated values based on 2000 repetitions.

| $b$  | $m$ | $m_0$ | $m_1$ | $p_{\text{Approx}}$ | Monte Carlo |
|------|-----|-------|-------|----------------------|-------------|
| 4.71 | 500 | 1     | 50    | 0.05                 | 0.053       |
| 4.60 | 500 | 1     | 100   | 0.10                | 0.103       |
| 4.77 | 500 | 1     | 100   | 0.05                 | 0.054       |
| 4.71 | 500 | 3     | 100   | 0.05                 | 0.043       |
| 4.45 | 500 | 3     | 50    | 0.10                 | 0.108       |
| 4.68 | 300 | 1     | 299   | 0.050               | 0.049       |
| 4.76 | 400 | 1     | 399   | 0.051               | 0.049       |
| 4.83 | 500 | 1     | 499   | 0.050               | 0.047       |

Some numerical experimentation, not reported here in detail, suggests that the approximation (2.2) is also adequate. For example, for $m = 500$, the threshold $b = 4.34$ yields the probability 0.051, while simulations (2500) repetitions give the probability 0.045.

3 Confidence Regions

We continue to assume independent normal observations $X_1, \ldots, X_m$ with mean values forming a step function with jumps at $\tau_k$, $1 \leq k \leq M$ and variance equal to one. For a given value of $M$, we can use the likelihood ratio statistic to construct a joint confidence region for the change-points $\tau = (\tau_1, \ldots, \tau_M)$ or for the change-points and mean values $\mu = (\mu_1, \ldots, \mu_{M+1})$.

We use the inverse relation between confidence intervals and hypothesis tests. For testing a putative value of the positions of change points and the corresponding mean values, the maximum log likelihood ratio statistic is

$$T_{\tau,\mu} = \max_{0 < t_1 < \cdots < t_M < m} \left[ \sum_{k=1}^{M+1} \frac{(S_{t_k} - S_{t_{k-1}})^2}{2(t_k - t_{k-1})} - \sum_{k=1}^{M+1} \mu_k (S_{\tau_k} - S_{\tau_{k-1}}) - \frac{\mu_0^2}{2} (\tau_k - \tau_{k-1}) \right]$$

$$= \max_{0 < t_1 < \cdots < t_M < m} U_{t,\tau,\mu},$$

(3.1)

where $t = (t_1, \ldots, t_M)$ and $S_i = \sum_{j=1}^{i} X_j$ for $0 \leq i \leq m$. The $1 - \alpha$ confidence region consists of those $\tau$ and $\mu$ such that $T_{\tau,\mu} \leq b_{\tau,\mu}$ where

$$\mathbb{P}_{\tau,\mu}(T_{\tau,\mu} > b_{\tau,\mu}) = \alpha.$$  

(3.2)
If we are only interested in the confidence region of $\tau$ and treat $\mu$ as a nuisance parameter, the maximum log likelihood ratio statistic is

\[
T_\tau = \max_{t_1, \ldots, t_M} \sum_{k=1}^{M+1} \frac{(S_{t_k} - S_{t_{k-1}})^2}{2(t_k - t_{k-1})} - \sum_{k=1}^{M+1} \frac{(\tau_k - \tau_{k-1})^2}{2(\tau_k - \tau_{k-1})}.
\] (3.3)

See Section 4 of Siegmund (1988b) for the corresponding statistic for exponential families in the case of one change point. By sufficiency the conditional distribution of $T_\tau$ given $\{S_{\tau_k} : 1 \leq k \leq M + 1\}$ does not depend on $\mu$. Therefore, a $1 - \alpha$ confidence set for the change points is the set of $\tau$ such that $T_\tau \leq b_{\tau, S_{\tau_1}, \ldots, S_{\tau_M}}$, where

\[
P_{\tau}(T_\tau > b_{\tau, S_{\tau_1}, \ldots, S_{\tau_M}} | \tau, S_{\tau_1}, \ldots, S_{\tau_M}) = \alpha.
\] (3.4)

In the case there is known to be only one change point, i.e., $M = 1$, and for exponentially distributed random variables, the exact value of the left-hand side of (3.4) was given by Worsley (1986). For $M = 1$, asymptotic approximations for the left-hand side of both (3.2) and (3.4) were given by Siegmund (1988b) for exponential families. Since the asymptotic approximations in Siegmund (1988b) seem difficult to generalize to the case where $M \geq 2$, here we use a different approach to obtain asymptotic approximations for the left-hand side of both (3.2) and (3.4) for $M \geq 1$.

### 3.1 Tail approximations

To construct the joint confidence region for the change points and the corresponding parameters, for each $\tau$ and $\mu$, we need to find $b_{\tau, \mu}$ such that

\[
P_{\tau, \mu}(T_{\tau, \mu} > b_{\tau, \mu}) = \alpha
\]

where $T_{\tau, \mu}$ is defined in (3.1). The following theorem, the proof of which is deferred to Appendix B, gives an approximation to

\[
P_{\tau, \mu}(T_{\tau, \mu} > b)
\]

for large $b$. We suppose that the putative change-points are close enough to the true change-points so that the maximum can be taken over a relatively small neighborhood ($|t_k - \tau_k| \leq n_k$) of the putative change-points, i.e.,

\[
P_{\tau, \mu}(T_{\tau, \mu} > b) \sim P_{\tau, \mu}(\max_{t : |t_k - \tau_k| \leq n_k} U_{t, \tau, \mu} > b).
\]

The technical assumptions imposed in the theorem also ensure that the change-points are reasonably well separated from one another.
Theorem 3.1. Let \( \tau = \{\tau_1, \ldots, \tau_M\} \) and \( \mu = \{\mu_1, \ldots, \mu_{M+1}\} \) be defined as above. Define \( \delta_k = \mu_{k+1} - \mu_k \) for \( 1 \leq k \leq M \) and \( m_k = \tau_k - \tau_{k-1} \) for \( 1 \leq k \leq M + 1 \). Suppose that \( |\delta_k| \gg 1 \) and

\[
1 \ll b \ll n_k \ll (m_k \wedge m_{k+1})/b, \tag{3.5}
\]

where \( A \ll B \) means \( A/B \to 0 \). We have

\[
P_{\tau, \mu}(\max_{t:|t_k - \tau_k| \leq n_k} U_{t, \tau, \mu} > b) \sim P\left(\sum_{k=1}^{M} W_k + \frac{1}{2} \chi_{M+1}^2 > b\right), \tag{3.6}
\]

where \( U_{t, \tau, \mu} \) was defined in (3.1). \( W_1, \ldots, W_M, \chi_{M+1}^2 \) are independent, \( \chi_{M+1}^2 \) is a chi-squared random variable with \( M + 1 \) degrees of freedom, and for \( 1 \leq k \leq M \) the distribution of \( W_k \) is given by

\[
P(W_k > x) = 2\nu(|\delta_k|)e^{-x} - \nu^2(|\delta_k|)e^{-2x}, \quad \forall \ x \geq 0 \tag{3.7}
\]

for \( 1 \leq k \leq M \).

We have a similar approximation for the left-hand side of (3.4).

Theorem 3.2. Let \( T'_\tau \) be defined as in (3.3) with the maximum taken over \( |t_k - \tau_k| \leq n_k \) for \( 1 \leq k \leq M \). Define \( \delta_k = \hat{\mu}_{k+1} - \hat{\mu}_k \) for \( 1 \leq k \leq M \), \( \hat{\mu}_k = (S_{\tau_k} - S_{\tau_{k-1}})/(\tau_k - \tau_{k-1}) \) and \( m_k = \tau_k - \tau_{k-1} \) for \( 1 \leq k \leq M + 1 \). Suppose that \( |\delta_k| \gg 1 \) and

\[
1 \ll b \ll n_k \ll (m_k \wedge m_{k+1})/b. \tag{3.7}
\]

We have

\[
P_{\tau}(T'_\tau > b|S_{\tau_1}, \ldots, S_{\tau_M}) \sim P\left(\sum_{k=1}^{M} W_k > b\right)
\]

where \( W_1, \ldots, W_M \) are independent and have the same distributions as in Theorem 3.2 with \( \delta_k \) replaced by \( \hat{\delta}_k \).

It is easy to evaluate the distributions of \( \sum W_k \) and \( \sum W_k + \chi_{M+1}^2 \) by Fourier inversion, for values of \( M \) up to about 100, and by exponential tilting if still larger values of \( M \) are of interest. For simplicity assume that \( \delta_k = \delta \) for all \( k \). Let \( \nu = \nu(\delta) \) and \( \hat{f}(\lambda) = (1 - \nu)^2 + 2\nu/(1 + \sqrt{-1}\lambda) - 2\nu^2/(2 - \sqrt{-1}\lambda) \) denote the characteristic function of \( W_k \). Let \( \hat{g}(\lambda) \) be the characteristic function of a \( \chi_{M+1}^2 \) random variable. Finally, let \( h(\lambda) = \hat{f}^m(\lambda) * g(\lambda)[1 - \exp(-\sqrt{-1}\lambda b)]/(1 + \sqrt{-1}\lambda) \). Then the probability on the right hand side of (3.6) equals \( 1 - \int_0^\infty \text{Re}[h(\lambda)]d\lambda/\pi \).

In Table 2 we use simulations to check the accuracy of the approximation (3.6). The number of change-points is \( M = 2 \), and the length of the sequence of observations is \( m = 210 \). For different values of \( \delta_1 \) and \( \delta_2 \), we compute the
threshold $b$ such that the RHS \ref{eq:3.6} equals 0.05. The locations of change-points is $\tau_1 = 70, \tau_2 = 140$, and we let the mean values be $\mu_1 = 0, \mu_2 = \delta_1, \mu_3 = \delta_1 + \delta_2$. In Table 2, $\hat{p}$ denotes the probability on the LHS \ref{eq:3.6} with $n_k = m$ and is based on 10000 repetitions each. From Table 2, we can see that the approximation \ref{eq:3.6} is reasonably accurate for the range $1 < |\delta| < 2$. Smaller $|\delta|$ requires larger $m$ for the approximation to be reasonably accurate.

Table 2: Confidence Region Probabilities: $M = 2, \tau_1 = 70, \tau_2 = 140, m = 210$

| $\delta_1$  | $\delta_2$ | $b$     | $\hat{p}$ |
|------------|------------|---------|-----------|
| 0.75       | 0.75(-0.75)| 7.58    | 0.054(0.057) |
| 1          | 1(-1)      | 7.22    | 0.045(0.050) |
| 1.25       | 1.25(-1.25)| 6.91    | 0.047(0.046) |
| 1.5        | 1.5(-1.5)  | 6.62    | 0.046(0.047) |
| 2          | 2(-2)      | 6.14    | 0.042(0.047) |
| 1.5        | .75(-.75)  | 7.07    | 0.048(0.050) |

For a simple example of a confidence region for the change-points, we simulated $m = 161$ observations with changes in the mean value of size $\pm 2$ at observations 51, 91, and 121. In the first case $\hat{\delta} \approx 2$, which leads to a threshold of 4.95 for a 95% conditional confidence region, which consisted of the point estimators 51, 91, and either of 121 or 122. In a second simulation, the smallest estimate of $\hat{\delta}$ was approximately 1.5, which if used for all three change-points leads to a conservative threshold of 5.6. In this case the joint confidence region contained 7 combinations of values, for the three change-points: 50 or 51, 91, 92, or 93, and 121 or 122 in different combinations. When the size of the changes was decreased to $\pm 1.5$, with a threshold set to 5.6, the 95% joint confidence region extended up to 5 observations away from the change-points at 51 and 91, and a couple of observations away from 121; and as a reflection of the fluctuations in the sample paths of the random walk, the regions around the individual change-points were neither symmetric nor connected.

For applications to copy number variation, see Section 4.2.

### 3.2 Power

A similar argument as in the derivation of \ref{eq:3.6} (cf. Appendix B) can be used to compute approximately the power of the segmentation procedure based on \ref{eq:1.1}. When the size of a change in the mean value is $\delta$ and the (largest possible) background is $(i^*, k^*)$ for a change-point at $j^*$, we define
the marginal power to be
\[
1 - \Phi(b - \delta[h_1 h_2/(h_1 + h_2)]^{1/2}),
\]
(3.8)
where \( h_1 = j^* - i^* \), \( h_2 = k^* - i^* \). This is just the marginal probability that the statistic \( Z_{i,j,k} \) evaluated at the true change-point \( j = j^* \) with the largest possible background \( i = i^* \), \( k = k^* \) exceeds the threshold \( b \). A detection may also occur due to local perturbation of the values \( i^*, j^*, k^* \). The probability of such a detection can be approximated by
\[
2 \int_0^{b^2/2} \mathbb{P}\left\{ \sum_{i \in \{0,1,2\}} W_i > b^2/2 - x \right\} f(2x; 1, \lambda) dx,
\]
(3.9)
where \( f(\cdot; 1, \lambda) \) is the probability density function of a \( \chi^2 \) distribution with one degree of freedom and noncentrality parameter \( \lambda = \delta^2 h_1 h_2/(h_1 + h_2) \), \( W_0, W_1, W_2 \) are independent, \( W_0 \) is nonnegative and has the probability distribution \( \mathbb{P}\{W_0 > x\} = 2\nu(\Delta) \exp(-x) - \nu^2(\Delta) \exp(-2x) \) for \( x \geq 0 \) with \( \Delta = b\sqrt{1/h_1 + 1/h_2} \), and for \( i = 1, 2 \), \( W_i \) is nonnegative and has the distribution given by \( \mathbb{P}\{W_i > x\} = \nu(\Delta_i) \exp(-x) \) for \( x \geq 0 \) with \( \Delta_1 = \Delta/(1 + h_1/h_2) \) and \( \Delta_2 = \Delta/(1 + h_2/h_1) \). We use the term local power to denote the sum of the marginal power (3.8) and the perturbation (3.9). Similar approximations can be obtained for the pseudo-sequential procedure and for multidimensional statistics.

4 Simulations and Applications

In this section we report the result of numerical exercises involving simulated and real data to compare a number of different segmentation procedures, with emphasis on their efficiency to detect change-points without an excessive number of false positive errors. We consider only thresholding algorithms that nominally control the false positive error rate, although this control can break down under certain conditions iteration to find multiple change-points is required.

In addition to the procedures introduced above, we also consider two statistics that can be particularly useful to detect inherited CNV, where changes often occur in pairs, with one change being an increase in mean value and the other a decrease of the same magnitude. For this problem (i) the likelihood ratio statistic is suggested in Olshen et al. (2004), where their segmentation algorithm is called circular binary segmentation (CBS) and (ii) the multiscale (Multi) modification of (i) recommended by Frick, Munk and Sieling (2014) is designed to have more power to detect longer intervals than CBS, but with some loss of power to detect short intervals.

The log likelihood ratio (CBS) statistic for searching the interval \( (m_1, m_2) \) is proportional to
\[
\max_{m_1 < i < j \leq m_2} |Z_{i,j}|,
\]
(4.1)
where

\[ Z_{i,j} = \left\{ S_j - S_i - (j-i)[S_{m_2} - S_{m_1}] / (m_2 - m_1) \right\} / \left\{ (j-i)(1-(j-i)/(m_2 - m_1)) \right\}^{1/2}. \]  

The statistic Multi is modified by subtracting \( 2 \log \left[ 3 m (m_2 - m_1) / (j - i)(m_2 - m_1 - j + i) \right]^{1/2}. \) Significance thresholds are determined by approximations that are stated in Appendix C and derived by methods similar to those for the statistics described above.

Although these statistics have been suggested by others, our implementations of procedures based on (4.2) and Multi, which use “top-down” iteration beginning from \( m_1 = 0, m_2 = m, \) are somewhat different from those suggested by the originators of those procedures.

We begin by searching the entire interval of observations. When one change-point (respectively, a pair of change-points) is detected, the interval searched is divided into two (respectively, three subintervals), and those subintervals are searched for additional change-points. Since the methods are designed to detect change-points occurring in pairs, under various conditions, e.g., when there is only one change-point to be detected in a search interval, or when consecutive changes are both positive or both negative, one of the paired “detections” often suggests a change-point very near to one end-point of the search interval. This is usually a false detection that is easy to recognize and disregard, although the decision to disregard it has an element of subjectivity. To minimize this subjectivity in our simulations, after some experimentation we usually discard any detection having a distance to an end-point of the interval searched that is within 5% of the length of that interval. If both detections are within this distance, the one closer to an end-point is discarded. If they are equally distant from an end-point, the one to be discarded is chosen at random. While objective, this rule can in some cases lead to errors, so in practice we recommend making a subjective decision based on a careful examination of the data.

Although both CBS and Multi use top down iteration, which it is natural to conjecture may lead to false positives after several iterations, this does not appear to be a major problem. If a large interval is partitioned into smaller intervals by correctly detected change-points, the false positive probability for CBS for the initial interval is numerically very close to the sum of the probabilities for the subintervals, so the sum of the false positive probabilities for the small intervals is roughly the same as that of the initial search. For Multi, this sum is much less than the false positive probability of the initial search. It appears that for both of these statistics the main source of false positive errors arises, fortunately not too often, when a correct detection is paired with a false detection that is not close enough to an endpoint to be excluded.

It is also possible to give approximations for the local power for these statistics. For simplicity we consider only the CBS statistic in the case
where the background mean value is known and equals 0 before the first change-point at \( i \) and after the second change-point at \( j \). Assume that the magnitude of the change equals \( \delta \). Let \( n_0 = j - i \). Approximations and some calculus similar to that given in Section 3.2 lead to

\[
P_\delta \left\{ \max_{0 \leq i < j \leq m} \frac{|S_j - S_i|}{(j - i)^{1/2}} \geq b \right\} \approx \Phi(\delta n_0^{1/2} - b) + 2 \int_0^{b^2/2} \mathbb{P}(W_1 + W_2 \geq b^2/2 - x) f(2x; 1, \delta^2 n_0) dx,
\]

where \( f(\cdot; 1, \lambda) \) is the density function of the chi-squared distribution with 1 degree of freedom and noncentrality parameter \( \lambda \), and \( W_1, W_2 \) are independent and identically distributed nonnegative random variables with the distribution given by \( \mathbb{P}(W_i > x) = 2\nu(\Delta) \exp(-x) - \nu^2(\Delta) \exp(-2x) \) for \( x \geq 0 \) with \( \Delta = b/\sqrt{n_0} \). Similar results hold for the power of Multi and of Seq.

We do not consider in detail other top down iterative thresholding procedures that appear to have poorly controlled false positive error rates. One is the classical binary segmentation procedure of Vostrikova (1981), which has a false positive error probability that builds up very quickly with the number of iterations required. For example, suppose that we use the threshold of \( b = 3.0 \), which for \( m = 300 \) gives a global false positive probability of approximately 0.05 on the initial search, and assume that we correctly detect the four change-points of the first example in Table 3. Then the sum of the false positive probabilities searching for a fifth change-point in the intervals between those already detected is about 0.126, and it would be larger if more iterations are required. For similar reasons we also have omitted the thresholding procedure suggested by Aston and Kirch (2012), which is similar to CBS and Multi in the sense that it searches for a complementary pair of change-points; but the statistic \( S_j - S_i - (j - i)S_m/m \) is not standardized to obtain a statistic having a marginal distribution with unit variance. Its false positive probability is also poorly controlled when the procedure is iterated. In addition to poor control of false positive errors, these two procedures have little power to detect two near-by change-points, which occur frequently in the data motivating our studies, although this may not be regarded a serious liability in other scientific contexts where multiple changes in a short interval are not of interest.

### 4.1 Simulations

The first example in Table 3 is a modified version of a suggestion of (Olshen et al. (2004)), which those authors said was typical of the copy number data that motivated their study. There are three hundred observations and four change-points at 138, 199, 208, and 232, with mean values 0.0, 0.75, 2.5,
0.25, and 1.5 in the five gaps between change-points. According to the local power approximation of the preceding section, the segmentation procedure based on (1.1) has local power 0.77, 0.73, 0.91, and 0.85, respectively to detect these change-points; and in our simulations the change-point at 199 seems consistently to be the most difficult to detect. Failure to detect a change-point is marked in the table by a zero(0), and false positives by an asterisk(*).

The second example in the table is similar, but with all changes in a positive direction. The results are similar in spite of the fact that both CBS and Multi do not seem prepared to deal with this case.

In Table 3 our implementation of both (1.1) and (2.3) was to choose the values $j$ by minimizing the associated length of the background $k - i$ from among those values of $|Z_{i,j,k}|$ exceeding the threshold. If necessary, we enforced the condition mentioned above that the backgrounds not overlap. The other possibility mentioned above, to choose the largest value of the statistic, but then enforce the no overlap condition for the background values, frequently leads to more computation but only occasionally leads to a substantial difference in the segmentation. A possible attraction of this method is that one “pays in advance” to control the false positive errors, and hence can use a mixture of different methods to choose a segmentation, provided that the no overlap condition applies. For determining joint confidence regions for the change-points, we must condition on estimates the sizes of the changes in mean, and for that purpose the locally largest $|Z_i|$-values may be more useful.

Although the table contains only a few examples, several entries reinforce our intuition. The procedure based on (2.3) lacks power to detect both of two nearby changes by virtue of its requirement to use a symmetric background. Compared to (2.3), the procedure using (1.1) appears to be better at detecting nearby change-points at some loss of power to detect relatively isolated change-points. The procedure Multi fails to detect a short interval that CBS detects—not surprising since its justification involved an increase in power to detect longer intervals paid for by a decrease in power to detect very short intervals.

In Table 3 we see only a few false positive errors. Seq may make false positive errors when there is a large change. If a large change occurs at $j$, it may detect that change with the configuration $\hat{j} < j < \hat{k}$. The process is restarted at $i = \hat{j} + 1$ and may detect the same change a second time. This situation is usually easy to recognize subjectively. It could be prevented algorithmically by imposing a no overlap condition, but other simulations indicate that this would occasionally result in a failure to detect true change-points that occur very close together. We see for CBS and Multi a false positive error that occurred when searching an interval where there is only one true change-point to be detected. The statistics detect two, and the
Table 3: Examples of segmentations: $m = 300$, $b_{\text{Seq}} = 4.21$, $b_{\text{1.1}} = 4.68$, $b_{\text{2.3}} = 4.27$, $b_{\text{CBS}} = 4.23$, and $b_{\text{Multi}} = 1.51$. The initial mean value is 0. Locations of change-points and mean values after the change are as indicated.

| Procedure/Parameters | 138, 0.75 | 199, 2.5 | 208, 0.25 | 232, 1.5 |
|----------------------|-----------|----------|-----------|----------|
| Seq                  | 134       | 197      | 206       | 248      |
| 1.1                  | 164       | 198      | 206       | 248      |
| 2.3                  | 48*, 140  | 198      | 207       | 249      |
| CBS                  | 149       | 199      | 297       | 249      |
| Multi                | 149       | 199      | 208       | 249      |
| Seq                  | 127       | 199      | 209       | 230      |
| 1.1                  | 127       | 198      | 211       | 230      |
| 2.3                  | 130       | 0        | 211       | 230      |
| CBS                  | 135       | 199      | 212       | 231      |
| Multi                | 135       | 199      | 212       | 231      |

| Procedure/Parameters | 138, 0.75 | 199, 2.5 | 208, 4.75 | 232, 6.0 |
|----------------------|-----------|----------|-----------|----------|
| Seq                  | 134       | 197      | 206       | 232      |
| 1.1                  | 145       | 198      | 207       | 234      |
| 2.3                  | 134       | 0        | 207       | 234      |
| CBS                  | 140       | 199      | 208       | 235      |
| Multi                | 140       | 199      | 208       | 235      |
| Seq                  | 136       | 197      | 206       | 235      |
| 1.1                  | 137       | 0        | 207       | 231      |
| 2.3                  | 137       | 199      | 208       | 235      |
| CBS                  | 138       | 0        | 207       | 236      |
| Multi                | 138       | 0        | 207       | 236      |
| Seq                  | 129       | 198      | 209       | 231      |
| 1.1                  | 159       | 198      | 207       | 231      |
| 2.3                  | 131       | 198      | 0         | 231      |
| CBS                  | 130       | 199      | 208       | 232      |
| Multi                | 130       | 199      | 208       | 232      |

| Procedure/Parameters | 100, 3.0 | 103, -0.5 | 120, 1.8 | 200, 2.5 |
|----------------------|----------|-----------|----------|----------|
| Seq                  | 97       | 101       | 117      | 199      |
| 1.1                  | 97       | 102       | 119      | 199      |
| 2.3                  | 0        | 0         | 119      | 200      |
| CBS                  | 98       | 103       | 120      | 200      |
| Multi                | 0        | 0         | 120      | 200      |
| Seq                  | 96       | 101       | 118      | 199      |
| 1.1                  | 98       | 102       | 119      | 200      |
| 2.3                  | 0        | 104       | 119      | 200      |
| CBS                  | 100      | 103       | 120      | 201      |
| Multi                | 0        | 0         | 120      | 207      |
| Seq                  | 98       | 0         | 117      | 214      |
| 1.1                  | 99       | 101       | 122      | 214      |
| 2.3                  | 99       | 0         | 121      | 214      |
| CBS                  | 100      | 102       | 122      | 140*, 215|
| Multi                | 100      | 102       | 122      | 140*, 215|
incorrect detections are not eliminated by the 5% rule described above. Other simulations indicate that this is the most commonly occurring false positive error of those statistics.

As mentioned in Section 1, in studying CNV various authors starting with Olshen et al. (2004) have found technical artifacts in the form of local trends that tend to disrupt the idealized model of a step function mean value. The local trends appear to be affected primarily by CG content, which oscillates in a roughly sinusoidal fashion. To test robustness against these perturbations Olshen et al. (2004) suggest adding a low frequency sinusoid, which produces some degradation of performance. In Table 4, we report a very small simulation comparing (1.1) to CBS in the presence of a sinusoidal perturbation of the mean values. In the first three rows, the frequency and amplitude are larger than those suggested by Olshen et al. (2004). In the second three rows, the amplitude is still larger, the frequency is relatively small, and a random phase has been included. These and other simulations, not shown here, suggest that modest local trends lead to slight increases in the false positive rate of CBS (and Multi) and to slight decreases in the power of detection of all methods, but does not alter substantially their comparative strengths and weaknesses. The local trends in the last three rows have a large amplitude and small frequency. Without these local trends, the change-points would be easy to detect, and the up-down pairs are ideal for CBS. Indeed, each change-point is detected, but there is a striking increase in false positives for CBS (and Multi, data not shown).

Table 5 provides the outcomes of 1000 simulations for detecting $M$ change-points randomly located from 0 to 500. The sizes of the changes are normally distributed with mean value $2.5\xi$, where the values $\xi$ are independently $\pm 1$ with probability $1/2$ and variance 0.5. The first method uses the maximum $\max_{i,j,k}|Z_{i,j,k}|$, with segmentation based on the smallest value of $k - i$ for which the statistic exceeds the 0.05 level threshold $b_1 = 4.83$; the second is the sequential version described above, with the threshold 4.33; the third is the Wild Binary Segmentation procedure of Fryzlewicz (2014) with threshold $b_{\text{WBS}} = 4.565$. (This threshold is close to, but slightly different from the value $1.3[2\log(m)]^{1/2} = 4.58$ recommended by Fryzlewicz, which was presumably determined by numerical experimentation. Our threshold is the 0.15 significance threshold according to the approximation (2.1).) The fourth is the segmentation procedure based on (2.3) with the threshold 4.42. The last two procedures are CBS and Multi discussed above in this section.

Although the simple counts in Table 5 without an indication of accuracy of the detections are not definitive, as we see in Table 3 in most cases accuracy is less an issue than the errors of over or under detection.

The procedures based on (1.1) and (2.3) are the only ones that in theory have control over the false positive rate; and the simulations clearly show that the others make more false positives errors. Unsurprisingly (2.3) has problems with detection of near-by change-points. The procedure (1.1) pays
Table 4: Examples With Sinusoidal Local Trends: \( m = 200, b_{\text{lin}} = 4.54, b_{\text{CBS}} = 4.13 \). Format as in Table 3, but to simulate local trends \( 0.2 \sin(0.1k) \) is added to the \( k \)th mean value in the first three rows. For the second three rows the \( k \)th mean value is \( 0.4 \sin(0.05k + U) \), where \( U \) is a uniformly distributed random phase. For the third three rows, the local trend is \( 0.7 \times \sin(0.03 \times k + U) \).

| Procedure/Parameters | 60, 3.0 | 63, 0.2 | 83, 1.5 | 153, 2.4 |
|-----------------------|---------|---------|---------|---------|
| \( \text{L.1} \)       | 60      | 63      | 77      | 139     |
| CBS                   | 60      | 63      | 81      | 131     |
| \( \text{L.1} \)       | 60      | 68      | 83      | 146     |
| CBS                   | 60      | 63      | 83, 94* | 146     |
| \( \text{L.1} \)       | 60      | 63      | 0       | 147     |
| CBS                   | 60      | 63      | 83      | 153     |
| Procedure/Parameters  | 50, 3.0 | 53, 6.0 | 113, 5.0 | 118, 2.5 |
| \( \text{L.1} \)       | 50      | 53      | 113     | 0       |
| CBS                   | 0       | 53      | 113     | 0       |
| \( \text{L.1} \)       | 50      | 53      | 113     | 0       |
| CBS                   | 0       | 53      | 0       | 119     |
| \( \text{L.1} \)       | 50      | 53      | 0       | 117     |
| CBS                   | 16, 50  | 53      | 0       | 118     |
| Procedure/Parameters  | 50, 2.0 | 60, 0.0 | 135, 3.0 | 140, 0.0 |
| \( \text{L.1} \)       | 50      | 60      | 135     | 140     |
| CBS                   | 50      | 60      | 121, 135 | 140, 181* |
| \( \text{L.1} \)       | 50      | 60      | 135     | 140     |
| CBS                   | 47, 60  | 82     | 135     | 140, 184* |
| \( \text{L.1} \)       | 50      | 60      | 135     | 140     |
| CBS                   | 50      | 60      | 135     | 140     |

for its control over the false positive rate with less power than the others (except for NZ), although it seems to be about as powerful as CBS and Multi when change-points are relatively far apart. CBS and Multi behave very similarly, as do Seq and WBS.

The algorithm based on \( \text{L.1} \) requires of order \( m^3 \) computations, hence can be slow for large values of \( m \). A version with a relatively small value of \( m_1 \), which initially seemed appealing because it would be faster to evaluate and would exert some control over the detection of small changes, which often represent artifacts in the data, also behaved noticeably less well than the other procedures for these simulations. A perhaps more reasonable speed-up is based on the observation that for large changes that can be detected with small backgrounds, we want to estimate the background as accurately
Table 5: Random change-points, \( m = 500, b_1 = 4.83, b_{Seq} = 4.33, b_{WBS} = 4.565, b_{NZ} = 4.42, b_{CBS} = 4.36, b_{Multi} = 1.57 \). Table entries are number of times the correct number of change-points is detected, the number of under detections (false negative errors), and the number of over detections (false positive errors). E(asy) denotes the number of repetitions where all methods detected the correct number of change-points; I(mp ossible) gives the number of repetitions where no method detected the correct number of change-points.

| \( M \) | Min (\( k - i \)) | Seq | WBS | NZ | CBS | Multi | E/I |
|--------|-----------------|-----|-----|----|-----|-------|-----|
| 0      | 957/0/50        | 946/0/98 | 931/0/92 | 946/0/59 | 950/0/103 | 967/0/63 | 871/2 |
| 3      | 838/135/50      | 849/108/80 | 810/129/91 | 799/179/44 | 799/113/140 | 797/110/129 | 656/89 |
| 5      | 658/377/24      | 712/277/71 | 638/347/80 | 593/470/25 | 634/284/171 | 656/277/139 | 448/192 |
| 8      | 373/980/4       | 457/735/67 | 392/899/29 | 281/1192/4 | 433/669/157 | 426/704/124 | 184/380 |

as possible. But for relatively large backgrounds used to detect relatively small changes, determining the exact background does not seem to be important. Suppose then, that in considering a fixed value of \( j \), to determine an appropriate \( k \), we choose \( k = j + 1 \), then choose a new value of \( k \) recursively as the old value plus \( \max(1, [(k - j)/10]) \), where \([x]\) denotes the largest integer less than or equal to \( x \). Thus, for \( k - j < 20 \), we choose every integer, then every second integer for \( k - j < 30 \), etc. The computational complexity of this procedure is of order \( m (\log(m))^2 \ell^2 \), where \( \ell = 10 \). Other speed-ups of a similar nature are possible.

Table 6 gives a brief summary of the modified procedure of the preceding paragraph in comparison with wild binary segmentation.

Table 6: Random Change-points, \( m = 500, b_1 = 4.83, b_{WBS} = 4.565 \). Search algorithm modified as described in the text

| Number | Min \((k - i)\) | WBS |
|--------|----------------|-----|
| 3      | 82/17/2        | 81/15/5 |
| 5      | 64/39/6        | 60/37/9 |
| 8      | 37/90/4        | 36/78/9 |

4.2 Array CGH data

In this section we present examples involving change-points in copy number variation (CNV) from array CGH data.
We first consider the test cases GBM29 and GBM31 used by Lai et al. (2005), to compare different methods of segmentation. For GBM29, the total length of the sequence is 193. The theoretical 0.05 thresholds for the procedure based on (1.1) and the pseudo-sequential procedure are 4.53 and 4.07, while that for CBS is 4.12 and for Multi is 1.45. The estimated standard deviation is 0.76. Change-points are detected at

81, 85, 89, 96, 123, 133

by all methods.

For GBM31, the length of the sequence is 797. The estimated standard deviation is 0.38. All methods, except the multiscale statistic detect the same set of change-points, at

317, 318, 538, 727, 728.

The third change-point is a relatively small change apparently indicating a long region of loss of copy number; the first two and last two change-points are large spikes. Only one of the two is detected by the multiscale statistic, which is designed to favor detection of longer intervals.

We have also tested our methods on the BT474 cell line data from Snijders et al. (2003). See Pollack et al. (1999, 2002) for a different experimental technique involving BT474 and a discussion of the implications for breast cancer. This cell line has also been used by, e.g., Zhao et al. (2004), who based their experimental technique on SNPs rather than array CGH.

For a scan of the entire genome we detect 63 change-points with the statistic (1.1) at a 0.05 genome wide significance threshold of $b = 5.2$; and we detect 67 using the pseudo-sequential procedure with a threshold of 4.7. Since the estimated standard deviation of the observations can vary considerably from one chromosome to the next, we consider also several individual chromosomes.

We continue to use genome wide thresholds, which are 4.68 for CBS and 1.67 for Multi; but we now use standard deviations specific to each chromosome. Particularly interesting are chromosome 17, where an amplification at 17q23 appears to have implications for breast cancer, and chromosome 20, which appears to contain a large increase in copy number embedded in a modest increase in copy number. For chromosome 17, there are $m = 87$ observations, with an estimated standard deviation of 0.51. According to (1.1), Seq, CBS and Multi, there is an increase in copy number at the 35th observation (17q11.2-12), with a change back to baseline just two observations later. There is a second increase at the 50th observation (17q21.3) and a return to the baseline at the 66th (17q23). Chromosome 20 contains $m = 85$ observations, and the standard deviation is 0.59. The statistics (1.1), Seq, CBS, and Multi again agree and detect a decrease in copy number from the 38th (20q11.2) to the 52nd observation, followed by an increase from the
53rd (20q13) to the 68th (20q13.1). From the 69th observation there is an even larger increase until the 82nd (20q13.3), then a return to roughly the baseline value for the last three observations.

Also interesting are chromosomes 4, 5 and 11, all of which have several changes, and some of the changes are followed by a second change after only a few observations. On chromosome 4 there are 162 observations, and at the 0.05 global significance level $[1.1]$ and Seq detected changes at 7, 8, 59, 61, 141, 143, and 155. CBS and Multi detected the same changes with the exception of 143, which both missed. On chromosome 5 there were 99 observations, with changes detected by all four methods at 25, 45, 51, and 65. CBS and Multi also detected paired changes at 87 and 91. The first of these was missed by $[1.1]$, and both were missed by Seq. On chromosome 11 there are 181 observations and changes detected by all four methods at 91, 124, 139, 144, 162, 165. In this case Seq also detected changes at 6 and 163.

To illustrate our confidence region calculations, we consider Chromosome 3, where there are 85 observations and change-points are detected at 19, 39, and 44. The estimated size of the change at 44 is $\hat{\delta} = 2.25$, while the changes at 19 and at 39 are estimated to be substantially larger. For simplicity we (conservatively) use the single estimated difference, $\hat{\delta} = 2.25$, so from the theory developed above, the critical constant for a 95% joint conditional confidence region for the three change-points is 4.63. Using this threshold, a joint confidence region consists of the exact point estimates 19 and 39, and the union of 43, 44, and 45. For Chromosome 15 change-points are detected at observations 43 and 57, where the smaller change is estimated to be about 2.3 and the other only slightly larger. For the approximate threshold of $b = 3.6$, we found a 95% joint confidence region to consist of the four pairs 42 or 43 and 56 or 57. For Chromosome 20, where we detected change-points at 38, 52, 68, and 82, the smallest value of $\hat{\delta}$ is 2.1 at 68. Using this single estimator, we find that the critical constant for a 95% joint confidence region for four change-points is $b = 5.9$. The union of the values that in various 4-tuples form the joint confidence region are 38, 39, 51, 52, 66, 67, 68, and 82.

**Remark.** In studying copy number variation it is customary to plot the locus by locus measurements, which should be about equal to zero when the copy number is two, with positive values indicative of amplifications and negative values indicative of deletions. There may be advantages to plotting the consecutive partial sums also and looking for a change in slope to indicate an increase or decrease in copy number. This plot is substantially smoother, and changes in slope that are candidates for change-points in copy number are easy to see. The disadvantage is that it is sometimes difficult to infer the sections of normal copy number, which are regions where the slope is near zero although it seems that it is never exactly equal to zero.
5 Exponential Families

A natural generalization of the methods of this paper involve data from exponential families, where there usually is the option to pursue analogous methods or to use a normal approximation. We first develop the analogous theory and discuss the second possibility below.

Assume $X_1, \ldots, X_m$ are independent and from a one-parameter exponential family of distributions $\{F_\theta : \theta \in \Theta\}$ where

$$dF_\theta(x) = \exp(\theta x - \psi(\theta)), \quad x \in \mathbb{R}, \ \theta \in \Theta,$$

$u$ is a $\sigma$-finite measure on the real line and $\Theta$ is an open interval. For $0 \leq i < j < k \leq m$, the likelihood ratio statistic to test whether $j$ is a change-point in the local background $(i, k]$ is

$$\ell_{i, j, k} = (j - i) \sup_{\theta_1} (S_j - S_i - \psi(\theta_1)) + (k - j) \sup_{\theta_2} (S_k - S_j - \psi(\theta_2))$$

$$- (k - i) \sup_{\theta} (S_k - S_i - \psi(\theta)).$$

In the following, we use $P_\theta$ ($E_\theta$ resp.) to denote the probability (expectation resp.) calculated when $X_i \sim F_\theta, \ \forall \ i$. Following the proof of (2.1), we suggest the following approximation to the $p$-value of $\max_{i,j,k} \ell_{i, j, k}$:

$$P_\theta\left( \max_{m_0 \leq j-i, k-j \leq m_1} \ell_{i, j, k} \geq \frac{b^2}{2} \right)$$

$$\sim \varphi(b) \sum_{m_0 \leq n_1, n_2 \leq m_1, \ n_1 + n_2 \leq m} \frac{a(\theta_1, \theta_2) a(\theta_1, \theta_2) a(\theta_1, \theta_2)}{n_1 (\theta_1 - \theta)^2 \psi''(\theta_1) + n_2 (\theta_2 - \theta)^2 \psi''(\theta_2)}^{1/2}$$

(5.1)

where the third summation is over two pairs of $\theta_1 < \theta_2$, which are assumed to exist (see the remark below), solving

$$\left\{ \begin{array}{l}
\psi'(\theta_1) n_1 + \psi'(\theta_2) n_2 = \psi'(\theta)(n_1 + n_2), \\
n_1 \psi'(\theta_1) + n_2 \psi'(\theta_2) - \psi(\theta_1) - n_1 + n_2 |\theta \psi'(\theta) - \psi(\theta)| = b^2/2,
\end{array} \right.$$

and for $\theta_1 < \theta_2$,

$$a(\theta_1, \theta_2) = \exp\left(-\sum_{i=1}^{\infty} n^{-1} E_{\theta_2} e^{-[(\theta_2 - \theta_1) S_n - n(\psi(\theta_2) - \psi(\theta_1))]^+}\right).$$

We use Theorem 8.51 of Siegmund (1985) and Theorem A of Tu and Siegmund (1999) to compute $a(\theta_1, \theta_2)$ numerically for nonarithmetic and arithmetic random variables respectively.
Remark. For those $n_1$ and $n_2$ such that the solutions to (5.2) do not exist, we first find the smallest $\theta' > \theta$ such that the solutions to (5.2) with $\theta$ replaced by $\theta'$ exist. We denote the solutions by $\theta'_1$ and $\theta'_2$. Then the proposed approximation is the RHS of (5.1) with $\theta, \theta_1, \theta_2$ replaced by $\theta', \theta'_1, \theta'_2$ respectively, and multiplied by $\mathbb{P}_\theta(S_{n_1+n_2}/(n_1 + n_2) \geq \psi'(\theta'))$.

5.1 Simulations

We first consider the exponential distribution with rate $\lambda$. Observing that in (5.1), both the probability and its approximation do not depend on $\lambda$, we choose $\lambda = 1$ without loss of generality. We fix $m_0 = 1$. In Table 7 with different values of $m, m_1$ and $b$, $p$ denotes the RHS of (5.1) and $\hat{p}$ denotes the simulated $p$-value with 2000 repetitions. We see from Table 7 that our approximation to the $p$-values are reasonably accurate, especially when $m$ and $m_1$ are large. A normal approximation would also be quite reasonable, especially for larger $m_1$ and $m$. For example, for the last line of Table 7 our normal approximation gives the probability 0.053.

| $\lambda$ | $m$ | $m_1$ | $b$ | $p$ | $\hat{p}$ |
|-----------|-----|-------|-----|-----|---------|
| 1         | 500 | 50    | 4.72| 0.049| 0.061   |
| 1         | 500 | 100   | 4.78| 0.048| 0.053   |
| 1         | 1000| 100   | 4.95| 0.047| 0.048   |

Next, we consider the inverse Gaussian distribution with fixed shape parameter $\lambda = 10$. We fix $m_0 = 1$. With different values of the mean $\mu, m, m_1$ and $b$, $p$ denotes the RHS of (5.1) and $\hat{p}$ denotes the simulated $p$-value with 2000 repetitions. We can see from Table 8 that both the theoretical and simulated $p$-values are reasonably robust against the mean $\mu$.

| $\mu$ | $m$ | $m_1$ | $b$ | $p$ | $\hat{p}$ |
|-------|-----|-------|-----|-----|---------|
| 1     | 300 | 30    | 4.5 | 0.059| 0.053   |
| 5     | 300 | 30    | 4.5 | 0.041| 0.050   |
| 1     | 500 | 100   | 4.78| 0.049| 0.037   |
| 5     | 500 | 100   | 4.78| 0.035| 0.031   |
| 1     | 1000| 100   | 4.95| 0.049| 0.050   |
| 5     | 1000| 100   | 4.95| 0.036| 0.034   |

Since the computation of appropriate thresholds for non-normal expo-
ential families is somewhat complicated, one may also consider the use of normal approximations, which in these cases would work quite well. Following are two examples where a Gaussian approximation to the signed square root of the likelihood ratio statistic seems to perform admirably.

For the detection of CG rich regions in genomic studies, as mentioned in the introduction, the sequences are very long and the exact boundary between regions has little biological significance. Hence one often forms groups of consecutive Bernoulli variables. Following Ehaik, Graur and Josić (2010), we have used groups of 33 consecutive Bernoulli variables. Since the values of the Bernoulli parameters $p$ are usually neither extremely small nor extremely large, possibilities that might indicate a Poisson approximation, we have tentatively assumed that we can use the theory developed above for the normal distribution. Since the Bernoulli variances must be estimated locally in each homogeneous region, it turns out that the skewness of the binomial distribution when $p$ is not in the immediate neighborhood of 1/2 can make an approximation of the distribution of the scaled value of $[S_j - S_i - (j - i)(S_k - S_i)/(k - i)]$ by a normal distribution unsatisfactory, unless the size of the groups is relatively large. Consequently we have used the signed square roots of the log likelihood ratio statistics, which behave very much like a Gaussian process. It turns out that simulations of this process indicate that the approximation is quite satisfactory and offer no new insights, so we omit the details.

The copy number data discussed in this paper was all obtained by comparative genomic hybridization. To achieve greater resolution, many present day studies use sequence data (e.g., Zhang et al. 2016), which often utilize models built from Poisson processes. The simplest of these is concerned with detection of a change from a background rate for a Poisson process. Since the background rate varies with genomic position due to variation in sequencing depth, local detection procedures along the lines of (1.1) may be useful. Like the binomial distribution, to detect changes in the rate of a Poisson process, simulations support an approximation based on a normal approximation to the signed square root of the (generalized) log likelihood ratio statistic. For 500 observations, $b = 4.83$, and the mean of the Poisson distribution equal to 10, 400 simulations gave the significance value 0.0475, when our normal approximation gives the value 0.05. Calculation of Kullback-Leibler information suggests that for detecting changes from 10 to 20 and back to 10 in well separated intervals, interval lengths of 6 and 7 are borderline detectable. Several simulations of this case involving two pairs of change-points lead to successful detections of all four change-points, while the differences between the estimates of the change-points and the true values totaled 1-3 observations.
5.2 Changes in a Normal Mean and Variance

An interesting, but considerably more complex example, is to allow for simultaneous changes to both the mean and variance (or mean vector and covariance matrix) of a sequence of independent, normally distributed observations. Although the formulation we have adopted, which assumes a constant value of the variance is much more common, and the copy number data considered above shows little evidence of heteroscedasticity within chromosomes the recent paper (Du, Kao and Kou (2016)), where the possibility of simultaneous changes in the mean and variance is considered, motivates the following brief discussion.

For \(0 \leq i < j \leq m\) let \(\ell_{i,j} = -0.5(j-i)\log(\sigma^2) - 0.5\sum_{i+1}^{j} (X_k - \mu)^2 / \sigma^2\) denote the log likelihood of \(X_{i+1}, \ldots, X_j\), and let \(\hat{\ell}_{i,j} = -0.5(j-i)\log(\hat{\sigma}_{i,j}^2) - 0.5\sum_{i+1}^{j} (X_k - \bar{X}_{i,j})^2 / \hat{\sigma}_{i,j}^2\) denote the log likelihood with parameters replaced by estimators. When the estimators are the maximum likelihood estimators, the generalized likelihood ratio statistic (which reduces to one-half the square of (1.1) in the case of known \(\sigma^2 = 1\)) is \(\hat{\ell}_{i,j} + \hat{\ell}_{j,k} - \hat{\ell}_{i,k}\), maximized over \(i < j < k\). Necessarily we must take the minimum values of \(j-i\) and \(k-j\) at least equal to \(m_0 = 2\). If one is interested in detecting changes occurring as close together as those studied above, this maximum likelihood ratio statistic is very unstable when there are no changes and \(j-i\) or \(k-j\) is small, since the maximum likelihood estimator of \(\sigma^2\) can with substantial probability assume very small values. The consequence is that a suitable threshold to control the rate of false positives must be so large that the statistic has very poor power to detect changes, and this problem persists even when \(m_0\) is substantially larger than 2.

A device to ameliorate this problem that maintains the invariance of the likelihood ratio statistic under scale and location changes is to subtract a small constant \(c/2\) from the sample size in the denominators of the estimators \(\hat{\sigma}_{i,j}^2\) and \(\hat{\sigma}_{j,k}^2\), and subtract \(c\) from the denominator of \(\hat{\sigma}_{i,k}^2\). Then with these new estimators (denoted by a tilde) use the statistic \(-0.5c/2\log(\tilde{\sigma}_{i,j}^2) - 0.5c/2\log(\tilde{\sigma}_{j,k}^2) - 0.5c\log(\tilde{\sigma}_{i,k}^2)\). In simulations we have found that with \(m_0 = 2\) and \(c \approx 2.7\), this statistic has a false positive rate approximately the same as a two dimensional version of (1.1), for which the significance level and power approximations of this paper are easily adapted. A similar result holds for the corresponding CBS statistic. If the variance changes by a factor of \(1 + \Delta\), the difference in mean values, scaled to unit standard deviation, is \(\delta\), and \(\pi\) denotes the fraction of observations at unit variance before a change-point, rough law of large numbers arguments indicate a noncentrality parameter in large samples proportional to

\[
\pi(1 - \pi) \log(1 + \pi(1 - \pi)\delta^2 + (1 - \pi)\Delta) - (1 - \pi) \log(1 + \Delta)
\]

for the two dimensional statistic.
If in fact there is no change in the variance the marginal power of the two dimensional statistic to detect a change-point is approximately 0.2 - 0.3 less than the power of (1.1). When the variance does change, theoretical calculations and simulations suggest that there is a complex tradeoff that depends on the size of the changes in variance and the relative locations of the various change-points. Finally, there is also the issue that the likelihood ratio statistic that tests for a change in both mean and variance will not be as robust against excess kurtosis as a statistic that tests only for a change in mean value.

Following are the results of a few simulations that indicate the complexity of the problem. The statistics considered are the two-dimensional statistic suggested in this section, the statistic (1.1), and a modified version of (1.1), designed to compensate for the possibility that (1.1) has an excess of false positives. Since (1.1) estimates an average variance, if there is a sub-interval where the variance is much larger than that average variance, the statistic (1.1) will use an inappropriately small variance estimate, which may lead to false positives. The modification of (1.1) is as follows: for any $i < k$, when searching for a putative change-point in $[i, k]$, standardize the process by the estimated (maximum likelihood) variance of the observations $X_i, \ldots, X_k$. If there is a change-point in the interval, the maximum likelihood estimate may be positively biased, but other possibilities appear to be too unstable when the interval is short. Simulations indicate that the thresholds suggested by Theorem 1 are conservative.

In Table 9 the false positive in the sixth row is presumably a reflection of the fact that in the interval between 110 and 135 the variance of the observations is substantially larger than the “average variance” used by (1.1). Although we did not observe this in a number of other simulations, not reported here, this possibility of an inflated false positive error rate appears to be one of the principal disadvantages of using the unmodified (1.1), which otherwise seems to perform very well. The last five rows were based on the test case suggested by Du, Kao and Kou (2016) following an earlier suggestion of Lai et al. (2005), but we have reduced the signal to noise ratio to make more difficult what otherwise would be easy detections. In those last five rows we see the effect on the two dimensional statistic of the constant $c \approx 2.7$, which was introduced to reduce false positive errors in short test intervals, but here has an adverse effect on the power. For the modified version of (1.1), which often behaves quite similarly to the two dimensional statistic, the loss of power is presumably due to estimating the variance locally, which leads to large positive biases in (short) intervals containing change-points.

Since multiscale methods are designed to favor detection of change-points in longer over shorter intervals, it is natural to ask if imposition of a multiscale penalty on the square root of the likelihood ratio statistic would work here. Some numerical experimentation suggests that the penalty $[4 \log(3m/\min(j - i, k - j))]^{1/2}$ allows one to control the false positive rate,
Table 9: Changes in Mean and Variance: \( m = 200 \), Threshold for (1.1) and for the modification suggested above is \( b_1 = 4.54 \); threshold for the two dimensional statistic is \( b_2 = 4.97 \). Detected change-points are as noted for (1.1), for the modification indicated in the text (denoted by an asterisk), and for the two dimensional statistic suggested in this Section, respectively. False positive errors are denoted by an asterisk.

| \( \tau \)       | \( \mu \)       | \( \sigma \)       | (1.1)  | (1.1)* | 2-D  |
|------------------|------------------|------------------|--------|--------|------|
| 38,88,108,132    | 1.1,2.7,1.0,2.5  | 1.1,1.8,1.1,1.7  | 0, 88,104,132 | 0.86, 0.132 | 0, 88,0,133 |
| 38,88,108,132    | 1.1,2.7,1.0,2.5  | 1.1,1.8,1.1,1.7  | 39,86,106,135 | 39,86,106,0 | 39,88,107,0 |
| 38,88,108,132    | 1.1,2.7,1.0,2.5  | 1.1,1.8,1.1,1.7  | 0,0,0,132     | 37,0,0,132  | 69,82,0,0 |
| 38,88,108,132    | 1.1,2.7,1.0,2.5  | 1.1,1.8,1.1,1.7  | 0,90,108,134  | 36,90,0,134  | 36,84,0,134 |
| 30,80,110,135    | 1.5,0.5,2.5,1.0  | 1.5,1.0,2.0,1.2  | 0,0,110,134   | 0,0,110,0   | 0,0,110,136 |
| 30,80,110,135    | 1.5,0.5,2.5,1.0  | 1.5,1.0,2.0,1.2  | 30,74,110,115*,132 | 30,74,110,132 | 30,77,110,133 |
| 30,80,110,135    | 1.5,0.5,2.5,1.0  | 1.5,1.0,2.0,1.2  | 30,0,110,134  | 30,0,110,134 | 30,0,110,134 |
| 48,50,150,154    | 4.0,0.0,4.0,0.0   | 2.0,1.0,2.0,1.0  | 48,50,150,154 | 0.0,150,153 | 0,0,150,155 |
| 48,50,150,154    | 4.0,0.0,4.0,0.0   | 2.0,1.0,2.0,1.0  | 48,50,150,154 | 48,50,150,154 | 48,50,150,155 |
| 48,50,150,154    | 4.0,0.0,4.0,0.0   | 2.0,1.0,2.0,1.0  | 0.0,150,155   | 0,0,150,155 | 0,0,150,154 |
| 48,50,150,154    | 4.0,0.0,4.0,0.0   | 2.0,1.0,2.0,1.0  | 48,50,149,154 | 48,50,0,0   | 48,50,0,0 |
| 48,50,150,154    | 5.0,0.0,5.0,0.0   | 2.0,1.0,2.0,1.0  | 48,50,150,154 | 48,50,150,154 | 0,0,150,155 |

and the multiscale statistic performs about as well in these examples as the two dimensional statistic defined above.

6 Simulations for Confidence Intervals

In order to illustrate the size of the joint confidence regions introduced in Section 3, we consider in Table [10] some parameter settings related to Table 3. The upper part of the table, like Table [2] gives the estimated coverage probability based on 10000 simulations for examples where the threshold \( b \) has been selected so our theoretical approximation gives the probability 0.05. The lower part of the table gives the probability from 1000 simulations that the indicated values of \( t_1 \), \( t_2 \) are not contained in the confidence region. We have chosen values of \( t_i \) for which this probability is about 0.5, so one can regard the difference between \( t_i \) and \( \tau_i \) as a rough measure of the size of the confidence region when all other parameters are set to their correct values.

The rows beginning with 0.65 are particularly interesting, since they show that the relatively small change at \( \tau_1 = 138 \) compared with very large change at \( \tau_2 = 225 \) leads to substantially more uncertainty in the value of \( \tau_1 \) com-
pared to the value of $\tau_2$.

Table 10: Likelihood ratio based joint confidence intervals. $\hat{p}$ is the simulated probability that the parameters $t_1$ and $t_2$ are rejected when the true parameter values are $\tau_1$ and $\tau_2$. Nominal confidence level is 0.05. Simulations are based on 10000 (1000) repetitions in the first four (last 12) rows.

| $\delta_1$ | $\delta_2$ | $b$  | $\tau_1$, $\tau_2$ | $t_1$, $t_2$ | $\hat{p}$ |
|------------|------------|------|---------------------|--------------|-----------|
| 2.13       | 1.33       | 6.4  | 9, 33               | 9, 33        | 0.049     |
| 2.5        | 4.0        | 5.35 | 87, 104             | 87, 104      | 0.051     |
| 0.65       | 2.5        | 6.65 | 138, 225            | 138, 225     | 0.047     |
| 1.73       | 2.13       | 6.23 | 57, 66              | 57, 66       | 0.049     |
| 2.13       | 1.33       | 6.4  | 9, 33               | 7, 33        | 0.59      |
| 2.13       | 1.33       | 6.4  | 9, 33               | 11, 33       | 0.58      |
| 2.13       | 1.33       | 6.4  | 9, 33               | 9, 29        | 0.47      |
| 0.65       | 2.5        | 6.65 | 138, 225            | 9, 37        | 0.44      |
| 0.65       | 2.5        | 6.65 | 138, 225            | 138, 227     | 0.75      |
| 0.65       | 2.5        | 6.65 | 138, 225            | 138, 223     | 0.73      |
| 0.65       | 2.5        | 6.65 | 138, 225            | 120, 225     | 0.49      |
| 0.65       | 2.5        | 6.65 | 138, 225            | 156, 225     | 0.46      |
| 2.5        | 4.0        | 5.35 | 87, 104             | 87, 102      | 0.43      |
| 2.5        | 4.0        | 5.35 | 87, 104             | 87, 106      | 0.44      |
| 2.5        | 4.0        | 5.35 | 87, 104             | 86, 104      | 0.89      |
| 2.5        | 4.0        | 5.35 | 87, 104             | 88, 104      | 0.89      |

6.1 Comparison with other confidence intervals

Frick, Munk and Sieling (2014) suggested a different method to construct a confidence region jointly for the change-points and the mean values of the observations in the segments connecting those change-points. For each candidate set of change-points $\tau$ and mean values $\mu$, they suggest an application of their multiscale statistic

$$\max \left( \frac{|S_j - S_i - (j-i)\mu|}{(j-i)^{1/2}} - [2 \log(3m/(j-i))]^{1/2} \right)$$

(6.1)

where the maximum is taken over all $i < j$ within one of the segments of $(0, \tau_1], \ldots, (\tau_M, m]$, and $\mu$ is the hypothesized mean value in the segment. This is in effect a test of the hypothesis that there are no change-points in the hypothesized segments $(0, \tau_1], \ldots, (\tau_M, m]$ and the mean values are as hypothesized. Worsley (1980) discusses a similar idea under the assumption that there is a single change-point, and one is interested only in a confidence region for the change-point, not a joint confidence region for change-points.
and means. (Note that our approximation (7.16) allows us to condition on the sum of the observations in the interval under investigation and hence use these ideas to obtain joint confidence regions for the change-points alone.)

It is difficult to make a comparison of the two methods. In Table 11 we compare our confidence region defined by (3.2) with that using (6.1) in a small number of examples. We set $m = 200$, $\tau_1 = 50$, $\tau_2 = 100$ and consider values of the $\delta_i$ that are large enough that most of the time we will detect two change-points. The problem becomes one of locating them and estimating the mean values. For our confidence regions, we choose the thresholds $b_1 = 7.2$ so that the probability in (3.6) equals 0.05. This threshold was confirmed by simulation. Moreover, for the statistic (6.1), we chose the threshold $b_2 = 1.44$ for which a 20000 repetition simulation experiment gave the probability 0.05. This threshold is slightly larger than the theoretical approximation 1.41.

Since a direct comparison of these regions in terms of size is conceptually complicated and technically demanding, we use the relation of confidence regions to hypothesis testing to compare them in terms of power. Under specific hypothetical, but incorrect, values of the change-points and mean values the power of the test of the true values represents the probability that the hypothetical values do not lie in the confidence region. Hence the procedure with larger power is preferred. From Table 11 it seems clear that for the parameter settings analysed, the likelihood ratio procedure is preferable.

Table 11: Power to Detect Departure from True Parameter Values: $\tau = (50, 100)$ and $\mu$ as given; $t$ and $\xi$ are hypothesized values of $\tau$ and $\mu$. The subscript 1 indicates the likelihood ratio procedure, while 2 indicates the procedure based on (6.1). Simulations are based on 10000 repetitions.

| $\mu$      | $\xi$      | $t$     | Power\textsubscript{1} | Power\textsubscript{2} |
|------------|------------|---------|------------------------|------------------------|
| 0.0,1.0,0.0| 0.0,1.0,0.0| 55,95   | 0.64                   | 0.08                   |
| 0.0,1.0,0.0| 0.1,0.9,-0.2| 55,95   | 0.87                   | 0.40                   |
| 0.0,1.0,0.0| 0.1,0.9,-0.2| 40,100  | 0.75                   | 0.32                   |
| 0.0,1.2,2.0| 0.0,1.2,2.0| 47,105  | 0.47                   | 0.044                  |
| 0.0,1.2,2.0| 0.0,1.5,1.9| 47,105  | 0.75                   | 0.32                   |
| 0.0,1.5,0.75| 0.1,1.4,0.9| 40,97   | 0.96                   | 0.69                   |
| 0.0,1.5,0.75| 0.0,1.5,0.75| 44,98   | 0.81                   | 0.32                   |
| 0.0,1.2,-0.1| 0.1,1.1,0.1| 48,103  | 0.68                   | 0.22                   |
| 0.0,1.1,0.1 | -0.2,1.0,0.0| 52,115  | 0.91                   | 0.44                   |
| 0.0,1.0,2.0 | -0.1,1.1,2.1| 45,110  | 0.87                   | 0.24                   |
7 Discussion

We have studied local thresholding procedures for segmenting sequences of independent random variables subject to change-points in the mean. For subsets of intervals \((i, k)\) a statistic \(Z_{i,j,k}\) for \(i < j < k\) is studied to see if there is evidence of a change-point at \(j\), by comparing values of the statistic with a threshold designed to control the probability of a false positive error. Our pseudo-sequential procedure, leaves \(i\) fixed at 0 or at the most recently discovered candidate change-point, then sequentially with respect to \(k\) examines \(\max_{i<j<k} Z_{i,j,k}\) until it exceeds a suitable threshold. The statistic based on (1.1) has better false positive control, although it requires a relatively large threshold, and hence loses some power compared to the pseudo-sequential version.

Our suggested procedures are compared to several other threshold based procedures that attempt to control, with varying degrees of success, the false positive error rate: (i) the Wild Binary Segmentation procedure of Fryzlewicz (2014), (ii) the SaRa procedure of Niu and Zhang (2012), (iii) the CBS procedure of Olshen et al. (2004), and (iv) a related iterative threshold based implementation of the statistic of Frick, Munk and Sieling (2014). Each of these methods has strengths and weaknesses, some obvious, others not so obvious. The procedures (i), (iii), (iv), and our pseudo-sequential procedure exert reasonable control over the false positive rate and have good power of detection. The statistics (1.1) and (ii) provide strict asymptotic control of the false positive rate, but have somewhat less power. In particular, (ii) suffers a severe loss of power when change-points are close together. In this regard, (iii) and (iv) show expected power advantages/disadvantages, with (iii) performing better in detecting near-by change-points of large amplitude and (iv) performing better in detecting distant change-points of small amplitude. Our iterative thresholding implementation of (iv) is based on the approximation (7.16) and is quite different from the algorithm suggested in Frick, Munk and Sieling (2014). In spite of being designed to detect relatively long intervals of small amplitude at the expense of less power to detect short intervals of large amplitude, the multiscale statistic of Frick, Munk and Sieling (2014) performed very well in our examples where there is a preponderance of short intervals. In problems having a different distribution of long and short intervals it may prove even more useful. The method of Niu and Zhang (2012) performs well when the change-points are well separated, but poorly when they are close together.

We have used the likelihood ratio statistic to obtain approximate confidence regions for the locations of the change-points or jointly for the mean values and the locations. Numerical examples suggest that for change-points of large amplitude our methods provide more accurate estimates than the methods of Frick, Munk and Sieling (2014), although our asymptotic control of the confidence level deteriorates if the sizes of the changes are not large.
We have assumed the variance of the observations is known, since we are typically dealing with large sample sizes, but estimating the variance requires some thought. Since the sample variance is an inflated estimator in the presence of change-points, the use of which leads to a loss of power, we have used one-half the average of squared differences of consecutive observations. However, if consecutive observations are positively correlated, this estimator will be negatively biased, while the usual sample variance may still provide a reasonable estimate of the variability of individual observations. We hope to investigate this issue in the future.

We have provided a brief discussion of detecting simultaneous changes in a normal mean and variance, but our analysis to date suggests that the problem is quite complicated and requires additional study.

Appendix A

In this appendix, we prove Theorem 2.1. Theorem 2.2 follows from the same arguments and therefore its proof is omitted. The claims stated in the proof will be proved below.

Proof of Theorem 2.1. Denote the right-hand side of (2.1) by \( p \). Rewrite \( p \) as

\[
p = \frac{\varphi(b)}{4b} \sum_{u, v \in \{1, \ldots, m\}: u + v \leq m} \left( m - u - v \right) \left\{ \frac{b^6}{uv(u + v)} \nu\left[ b\left( \frac{u}{v(u + v)} \right)^{1/2} \right] \nu\left[ b\left( \frac{v}{u(u + v)} \right)^{1/2} \right] \nu\left[ b\left( \frac{u + v}{uv} \right)^{1/2} \right] \right\}.
\]

It was shown in Siegmund (1985) that \( \nu(x) = \exp(-cx) + o(x^2) \) as \( x \to 0 \) for \( c \approx 0.583 \), while \( x^2 \nu(x)/2 \to 1 \) as \( x \to \infty \). Therefore, the term inside the curly brackets above is bounded. Hence

\[
p \approx b^5 \varphi(b) \to 0,
\]

where we used the assumption that \( m \approx b^2 \).

Fix a sufficiently small constant \( c_0 \). We will prove first that

\[
P\{ \max_{0 \leq i < j < k \leq m \atop j-i, k-j \geq c_0 b^2} Z_{i,j,k} \geq b \} \sim \frac{1}{8} b^5 \varphi(b) \sum_{u, v \in \{1, \ldots, m\}: u + v \leq m} \frac{(m - u - v)}{uv(u + v)} \nu\left[ b\left( \frac{u}{v(u + v)} \right)^{1/2} \right] \nu\left[ b\left( \frac{v}{u(u + v)} \right)^{1/2} \right] \nu\left[ b\left( \frac{u + v}{uv} \right)^{1/2} \right].
\]

(7.2)
We write
\[
\mathbb{P}\left( \max_{0 \leq i < j < k \leq m} Z_{i,j,k} \geq b \right)
= \sum_{0 \leq i < j < k \leq m} \mathbb{P}(Z_{i,j,k} \geq b, Z_{i,j,k} = \max_{0 \leq r < s < t \leq s, t \geq c0^2} Z_{r,s,t})
= \sum_{0 \leq i < j < k \leq m} \int_{0}^{\infty} \mathbb{P}(\max_{0 \leq r < s < t \leq s, t \geq c0^2} Z_{r,s,t} \leq b + x | Z_{i,j,k} = b + x) \mathbb{P}(Z_{i,j,k} \in b + dx) + R
\]
where \(C\) is a positive constant to be chosen in Claim 7.1. It is straightforward to verify that the remainder \(R\) is of smaller order than \(p\).

For \(c_0 b^2 \leq u, v \leq m\), define
\[
d_1 = d_1(u, v) = \frac{b}{2u\sqrt{\frac{1}{u} + \frac{1}{v}}},
\]
\[
d_2 = d_2(u, v) = \frac{b}{2\sqrt{\frac{1}{u} + \frac{1}{v}}},
\]
and
\[
d_3 = d_3(u, v) = \frac{b}{2v\sqrt{\frac{1}{u} + \frac{1}{v}}}.\]

Since \(u, v \asymp b^2\), we have \(d_i, u(2d_i) \asymp 1\) for \(i = 1, 2, 3\).

To prove that (7.2), we only need to show that for any \(C \log b \leq i < j < k \leq m - C \log b\) such that \(j - i, k - j \geq c_0 b^2\), we have
\[
\mathbb{P}(\max_{0 \leq r < s < t \leq s, t \geq c0^2} Z_{r,s,t} \leq b | Z_{i,j,k} = b) \sim \prod_{i=1}^{3} (2d_i^2)^{u(2d_i)}, \tag{7.3}
\]
where \(d_i\) is defined above with \(u = j - i, v = k - j\).

In the following we fix any \(i, j, k\) such that \(C \log b \leq i < j < k \leq m - C \log b\) and \(j - i, k - j \geq c_0 b^2\) and prove (7.3). Let \(u = j - i, v = k - j\), and let \(d_1, d_2, d_3\) be as above.

Claim 7.1. There exists a large enough constant \(C\) such that
\[
\mathbb{P}(\max_{0 \leq r < s < t \leq s, t \geq c0^2, (j - i) \vee (s - j) \vee (t - k) \geq C \log b} Z_{r,s,t} > b | Z_{i,j,k} = b) = o(1).
\]
¡From Claim 7.1, the maximum in (7.3) can be restricted to those \( r, s, t \) such that \(|r - i|, |s - j|, |t - k| \leq C \log b \).

Next, we note that given \( Z_{i,j,k} = b \), we have

\[
\frac{S_j - S_i}{j - i} = -2d_1(1 + o(1)) \quad \text{and} \quad \frac{S_k - S_j}{k - j} = 2d_3(1 + o(1)).
\] (7.4)

This, together with Theorem 1.6 of Diaconis and Freedman (1988) and the fact that \( \log b \ll m_0 \), implies that given \( Z_{i,j,k} = b \),

\[
X_{i+1}, \ldots, X_{i+C \log b}, X_{j-C \log b+1}, \ldots, X_j, X_{j+1}, \ldots, X_{j+C \log b}, X_{k-C \log b+1}, \ldots, X_k
\]

are asymptotically mutually independent Gaussian variables with variance 1, the first half of the X’s have mean \(-2d_1\) and the second half of the X’s have mean \(2d_3\). Let us first consider the case \( r = i, s = j \) and \( k < t \leq k + C \log b \) in (7.3). Note that \( Z_{i,j,k} = b \) and \( Z_{i,j,t} \leq b \) are equivalent to

\[
u(S_k - S_j) - v(S_j - S_i) = buv \sqrt{\frac{1}{u} + \frac{1}{v}}
\] (7.5)

and

\[
u(S_t - S_k + S_k - S_j) - (v + t - k)(S_j - S_i) \leq bu(v + t - k) \sqrt{\frac{1}{u} + \frac{1}{v + t - k}}
\] (7.6)

Subtracting (7.5) from (7.6) and using Taylor’s expansion and (7.4), we have that given \( Z_{i,j,k} = b \), \( Z_{i,j,t} \leq b \) is equivalent to

\[
\sum_{l=1}^{t-k} [X_{k+l} - d_3(1 + o(1))] \leq 0.
\]

Therefore,

\[
P(\max_{k < t \leq k + C \log b} Z_{i,j,t} \leq b | Z_{i,j,k} = b)
\]

\[
P(\max_{1 \leq l \leq C \log b} (X_{k+l} - d_3(1 + o(1))) \leq 0).
\]

Note that \( X_{k+l} : l \geq 1 \) are i.i.d. \( \sim N(0, 1) \). Using the union bound, we have

\[
P(\max_{l > C \log b} (X_{k+l} - d_3(1 + o(1))) > 0) = o(1).
\]

Therefore,

\[
P(\max_{1 \leq l \leq C \log b} (X_{k+l} - d_3(1 + o(1))) \leq 0)
\]

\[
\approx P(\max_{l \geq 1} (X_{k+l} - d_3(1 + o(1))) \leq 0)
\]

\[
\approx \sqrt{2d_3 \nu^{1/2}(2d_3)},
\]

33
where the last equation is by Corollary 8.44 of Siegmund (1985).

Similar arguments for the other cases show that given $Z_{i,j,k} = b$, the event

$$\max_{0 \leq r < s < t \leq m} Z_{r,s,t} \leq b$$

is asymptotically the same as the event that six random walks starting from 0 and stays below 0 before time $C \log b$. These random walks are asymptotically independent and have independent Gaussian increments with variance 1 and means $-d_1, -d_1, -d_2, -d_2, -d_3, -d_3$ respectively. Therefore,

$$P\left( \max_{0 \leq r < s < t \leq m} Z_{r,s,t} \leq b \big| Z_{i,j,k} = b \right) \approx 3 \prod_{i=1}^{3} (2d_i^2)^{\nu(2d_i)}.$$

This proves (7.3). Now that we have proved (7.2), (2.1) follows by the following claim and then by letting $c_0 \to 0$.

**Claim 7.2.** We have

$$P\left( \max_{0 \leq r < s < t \leq m} |Z_{i,j,k}| \geq b \big| Z_{i,j,k} = b \right) \sim 2P\left( \max_{0 \leq r < s < t \leq m} Z_{i,j,k} \geq b \right).$$

**Proof of Claim 7.1.** We use the union bound

$$P\left( \max_{0 \leq r < s < t \leq m} Z_{r,s,t} > b \big| Z_{i,j,k} = b \right) \leq \sum_{0 \leq r < s < t \leq m} P\left( Z_{r,s,t} > b \big| Z_{i,j,k} = b \right).$$

There are totally $O(b^6)$ terms in the summation. As argued in the proof of Theorem 2.1, $Z_{r,s,t} - Z_{i,j,k}$ is asymptotically a superposition of Gaussian random walks with constant negative drift and unit variance locally when $(r, s, t)$ is close to $(i, j, k)$. Therefore, each term in the summation is bounded by

$$C_1 \exp(-c_2 C \log b) = C_1 b^{-c_2 C},$$

where $C_1$ and $c_2$ are positive constants. Hence, the summation tends to 0 by choosing a large enough $C$. \[\Box\]
Proof of Claim 7.2. We write
\[
P \left( \max_{0 \leq i < j < k \leq m; \quad j-i, k-j \geq c_0 b^2} |Z_{i,j,k}| \geq b \right)
= P \left( \max_{0 \leq i < j < k \leq m; \quad j-i, k-j \geq c_0 b^2} Z_{i,j,k} \geq b \right) + P \left( \max_{0 \leq i < j < k \leq m; \quad j-i, k-j \geq c_0 b^2} \{-Z_{i,j,k}\} \geq b \right)
- P \left( \max_{0 \leq i < j < k \leq m; \quad j-i, k-j \geq c_0 b^2} Z_{i,j,k} \geq b, \max_{0 \leq r < s < t \leq m; \quad s-r, t-s \geq c_0 b^2} \{-Z_{r,s,t}\} \geq b \right).
\]

The first two terms are equal by symmetry. The third term is bounded by
\[
\sum_{0 \leq i < j < k \leq m; \quad j-i, k-j \geq c_0 b^2} P \left( \max_{0 \leq r < s < t \leq m; \quad s-r, t-s \geq c_0 b^2} \{-Z_{r,s,t}\} \geq b \bigg| Z_{i,j,k} \geq b \right).
\]

We only need to show that the conditional probability above tends to 0. We again use the union bound
\[
P \left( \max_{0 \leq r < s < t \leq m; \quad s-r, t-s \geq c_0 b^2} \{-Z_{r,s,t}\} \geq b \bigg| Z_{i,j,k} \geq b \right)
\leq \sum_{0 \leq r < s < t \leq m; \quad s-r, t-s \geq c_0 b^2} P \left( \{-Z_{r,s,t}\} \geq b \bigg| Z_{i,j,k} \geq b \right).
\]

There are totally \(O(b^6)\) terms in the summation, and each term is subgaussian in \(b\). Therefore, the conditional probability tends to 0.

Appendix B

In this appendix, we prove Theorem 3.1. Theorem 3.2 follows from the same arguments and therefore its proof is omitted. The claims stated in the proof will be proved below.

Proof of Theorem 3.1. We use \(C\) and \(c\) to denote positive constants, which may differ in different expressions.

We denote the probability on the right-hand side of (3.6) by \(p\). Note that
\[
p \geq P(W_1 > b) \geq ce^{-b}.
\]

We can decompose \(U_{t,\tau,\mu}\) as
\[
U_{t,\tau,\mu} = \sum_{k=1}^{M+1} (V_{t,k} + Y_k),
\]

35
where
\[ V_{t,k} := V_{t,k,\tau} = \frac{(S_{t_k} - S_{t_{k-1}})^2}{2(t_k - t_{k-1})} - \frac{(S_{\tau_k} - S_{\tau_{k-1}})^2}{2(\tau_k - \tau_{k-1})} \]
and
\[ Y_k := Y_{k,\tau,\mu} = \frac{(S_{\tau_k} - S_{\tau_{k-1}} - (\tau_k - \tau_{k-1})\mu_k)^2}{2(\tau_k - \tau_{k-1})}. \]

Given \( \tau \) and \( \mu \), \( \{2Y_k : 1 \leq k \leq M + 1\} \) are independent and identically distributed \( \chi^2(1) \) random variables. We have
\[
\mathbb{P}(\max_{t:|t_k - \tau_k| \leq n_k} U_{t,\mu} > b|\tau, \mu) = \int_0^{2b} \mathbb{P}(\max_{t:|t_k - \tau_k| \leq n_k} M+1 \sum_{k=1}^{M+1} V_{t,k} > b - \frac{y}{2} \sum_{k=1}^{M+1} Y_k = \frac{y}{2} \tau, \theta) f_{\chi^2_{M+1}}(y)dy \tag{7.7}
\]
\[ + \int_{2b}^{\infty} f_{\chi^2_{M+1}}(y)dy, \]
where \( f_{\chi^2}(\cdot) \) denotes the density function of a \( \chi^2(j) \) random variable. Under condition (3.3), \( Y_k \leq b \) implies that
\[
\frac{S_{\tau_k} - S_{\tau_{k-1}}}{\tau_k - \tau_{k-1}} = \mu_k + o(1), \quad 1 \leq k \leq M + 1. \tag{7.8}
\]

Claim 7.3. Conditioning on \( \{S_{\tau_k} : 1 \leq k \leq M + 1\} \) such that (7.8) is satisfied, we have, with probability \( 1 - o(p) \),
\[
\frac{S_{t_k} - S_{t_{k-1}}}{t_k - t_{k-1}} = \mu_k + o(1), \quad 1 \leq k \leq M + 1 \tag{7.9}
\]
for all \( t \) such that \( |t_k - \tau_k| \leq n_k \).

From Claim 7.3 in the following we can assume (7.9). For \( |t_1 - \tau_1| \leq n_1 \), we have
\[
\frac{S_1^2}{2t_1} - \frac{S_2^2}{2\tau_1} = \frac{1}{2}[(S_{t_1}/t_1)(t_1/\tau_1)^{1/2} + S_{\tau_1}/\tau_1][S_{t_1}(t_1/\tau_1)]^{1/2} - S_{\tau_1}]
\]
\[ = (\mu_1 + o(1))[S_{t_1} - S_{\tau_1} - (t_1 - \tau_1)\mu_1 + o(1)]. \]

Similarly, for \( 2 \leq k \leq M \),
\[
\frac{(S_{t_k} - S_{t_{k-1}})^2}{2(t_k - t_{k-1})} - \frac{(S_{\tau_k} - S_{\tau_{k-1}})^2}{2(\tau_k - \tau_{k-1})}
\]
\[ = (\mu_k + o(1))[S_{\tau_{k-1}} - S_{t_{k-1}} + (t_{k-1} - \tau_{k-1})\mu_k + o(1)] \]
\[ + (\mu_k + o(1))[S_{t_k} - S_{\tau_k} - (t_k - \tau_k)\mu_k + o(1)], \]

36
and

\[
\frac{(S_m - S_{tM})^2}{2(m - t_M)} - \frac{(S_m - S_{tM})^2}{2(m - \tau_M)} = (\mu_{M+1} + o(1))[S_{tM} - S_{tM} + (t_M - \tau_M)\mu_{M+1} + o(1)].
\]

Therefore,

\[
\max_{t: |t - \tau_k| \leq n_k} \sum_{k=1}^{M+1} V_{t,k} = \max_{t: |t - \tau_k| \leq n_k} \sum_{k=1}^{M} (-\delta_k)(1+o(1))[S_{t_k} - S_{\tau_k} - (t_k - \tau_k)\mu_{k} + \mu_{k+1} + o(1)]/2.
\]

**Claim 7.4.** Suppose \( S_{\tau_k} - S_{\tau_{k-1}} \) satisfies (7.8). Then, with probability \( 1 - o(p) \), \( \{X_i: \tau_{k-1} < i \leq \tau_k + n_k\} \) and \( \{X_i: \tau_k - n_k < i \leq \tau_k\} \) are asymptotically independent and identically distributed with distribution \( N(\mu_k, 1) \).

Let \( \{\xi_j\}_{j \geq 1} \) be independent and identically distributed as \( N(0, 1) \). \( \xi \) From \( n_k \delta_k^2 \gg b \) and \( p \geq c e^{-b} \), we have

\[
\sum_{n > n_k} \mathbb{P}(|\delta_k|((\sum_{j=1}^{n} \xi_j - n|\delta_k|)/2) \geq b - y/2) \leq C \sum_{n > n_k} e^{-\frac{1}{4}n\delta_k^2} = o(p).
\]

\( \xi \) From (7.10), Claim 7.4 and the above bound, we have

\[
\mathbb{P}(\max_{t: |t - \tau_k| \leq n_k} \sum_{k=1}^{M+1} V_{t,k} > b - y/2) \sim \mathbb{P}(\sum_{k=1}^{M} \tilde{W}_k > b - y/2)
\]

where \( \{\tilde{W}_k\}_{1 \leq k \leq M} \) are independent,

\[
\tilde{W}_k = \max\{\tilde{W}_k^-, \tilde{W}_k^+\},
\]

\( \tilde{W}_k^- \) and \( \tilde{W}_k^+ \) are independent and identically distributed, and

\[
\tilde{W}_k^- = \sup_{i > 0} |\delta_k|((\sum_{j=1}^{i} \xi_j - i|\delta_k|)/2).
\]

We choose \( y_1 \) and \( z \) such that \( 1 \ll z \ll \log(y_1) \ll \log \log(b) \). \( \xi \) From (8.49) of Siegmund (1985), we have

\[
\mathbb{P}(\tilde{W}_k > z) \sim \mathbb{P}(W_k > z).
\]

This, together with Claim 7.5 and Claim 7.6 below, proves the theorem.
Claim 7.5. We have
\[
\int_{2b-y_1}^{\infty} f_{x^2M+1}(y) dy = o(p).
\]

Claim 7.6. We have
\[
\mathbb{P}(\sum_{k=1}^{M} \tilde{W}_k > y_1/2, \min_{1 \leq k \leq M} \tilde{W}_k > z).
\]

Proof of Claim 7.3. Assume \(k = 2\). The general case follows from the same argument. It suffices to show that there exists \(a \rightarrow 0\) such that
\[
n_1n_2\mathbb{P}\left(\frac{|S_{t_2} - S_{t_1}|}{t_2 - t_1} \geq a \middle| S_{t_2} - S_{t_1} = 0\right) = o(p) \tag{7.12}
\]
for all \(t_1, t_2\) such that \(|t_1 - \tau_1| \leq n_1\) and \(|t_2 - \tau_2| \leq n_2\). Note that conditioning on \(S_{t_2} - S_{t_1} = 0\), the mean value of \((S_{t_2} - S_{t_1})/(t_2 - t_1)\) is 0 and by \(n_k \ll (m_k \wedge m_{k+1})\), the variance is bounded by \(C(n_1 + n_2)/m_2^2\). Therefore,
\[
\mathbb{P}\left(\frac{|S_{t_2} - S_{t_1}|}{t_2 - t_1} \geq a \middle| S_{t_2} - S_{t_1} = 0\right) \leq \frac{C\sqrt{(n_1 + n_2)}}{am_2}\exp\left[-\frac{a^2m_2^2}{2C(n_1 + n_2)} + \log(n_1) + \log(n_2)\right]. \tag{7.13}
\]
For this to be of smaller order than \(p\), we need to choose \(a\) such that
\[
\frac{a^2m_2^2}{2C(n_1 + n_2)} - \log(n_1) - \log(n_2) - b \rightarrow \infty.
\]
Such an \(a \rightarrow 0\) exists because \(\frac{m_2^2}{n_1 + n_2} \gg b\).

Proof of Claim 7.4. We only prove for the case \(k = 2\). The other cases follow from the same argument. Choose \(D\) such that
\[
D^2 \ll m_2 \text{ and } \frac{D^2}{n_1 + n_2} \gg b.
\]
Such a \(D\) exists because of (3.3). Define
\[
\tilde{S}_{n_1}' = \sum_{i=\tau_1+1}^{\tau_1+n_1} X_i \text{ and } \tilde{S}_{n_2}'' = \sum_{i=\tau_2-n_2+1}^{\tau_2} X_i.
\]
By straightforward calculations, we have
\[
\mathbb{P}(|\tilde{S}_{n_1}' + \tilde{S}_{n_2}'' - \mu_2(n_1 + n_2)| \geq D|S_{t_2} - S_{t_1} = \mu_2) \ll p,
\]
and conditioning on the complement event that \(|\tilde{S}_{n_1}' + \tilde{S}_{n_2}'' - \mu_2(n_1 + n_2)| < D, \{X_i : \tau_1 < i \leq \tau_1 + n_1\} \text{ and } \{X_i : \tau_2 - n_2 < i \leq \tau_2\} \text{ are asymptotically independent and identically distributed with distribution } N(\mu_2, 1). \]

38
Proof of Claim 7.5. Note from (3.7) that the pdf of $W_1$ for large $x$ is larger than that of $\chi^2_1/2$. Therefore, 
\[ p \geq c \mathbb{P}(\chi^2_{M+2} \geq 2b) \geq cb^{1/2} \mathbb{P}(\chi^2_{M+1} \geq 2b), \]
which is of higher order than 
\[ \mathbb{P}(\chi^2_{M+1} \geq 2b - y_1) \]
by the choice of $y_1$. \( \square \)

Proof of Claim 7.6. It suffices to show that for $M \geq 2$,
\[ \mathbb{P}(\min_{1 \leq k \leq M} \tilde{W}_k \leq z | \sum_{k=1}^{M} \tilde{W}_k > y_1/2) = o(1). \]
Note that $\mathbb{P}(\sum_{k=1}^{M} \tilde{W}_k > y_1/2) \asymp y_1^{M-1} e^{-y_1/2}$. Therefore, 
\[ \mathbb{P}(\min_{1 \leq k \leq M} \tilde{W}_k \leq z | \sum_{k=1}^{M} \tilde{W}_k > y_1/2) \leq M \mathbb{P}(\sum_{k=1}^{M-1} \tilde{W}_k > y_1/2 - z) \times \frac{My_1^{M-2} e^{-y_1/2 + z}}{y_1^{M-1} e^{-y_1/2}} = o(1) \]
by the choice of $z$. \( \square \)

Appendix C

In this appendix we describe our implementation of the threshold based methods CBS and Multi, which are designed to detect paired changes; and we give approximations for their false positive error control. The multiscale modification of the statistic (1.1) mentioned at the end of Section 1 can be studied by a similar analysis.

The slightly different statistics are given by 
\[ \max_{0 \leq j < j+n \leq m} Z_{j,n}, \] (7.14)
where 
\[ Z_{j,n} = \left| S_{j+n} - S_j - nS_m/m \right| \left[ n(1 - n/m) \right]^{1/2} - \{2\kappa \log[3m/n(1 - n/m)]\}^{1/2} \] (7.15)
and $\kappa = 0$ or $1$. The case $\kappa = 0$ is the likelihood ratio statistic, which is called CBS (circular binary segmentation) and was suggested in Olshen et al. (2004), where it was applied to copy number data. The case $\kappa = 1$ is the multiscale statistic of Frick, Munk and Sieling (2014), who argued that the
likelihood ratio statistic puts relatively too much power into the detection of short intervals of large amplitude at the cost of considerably less power to detect relatively long intervals of small amplitude.

In our implementation, if change-points are detected, say at $i$ and $j$, the process is iterated by using appropriately modified statistics to search the three subintervals of $[1, m]$ for additional change-points. Frequently, e.g., if there is only a single change-point to be detected in the initial (or subsequent) search interval or if consecutive change-points both increase or both decrease the mean, the maximizing values of $j, n$ in (7.14) will typically have either $j$ close to one of $j+n$ close to $m$, and in that case we declare that a single change-point has been detected. How close is a matter of subjective judgment, as discussed in Section 4.

If $(X_1, \ldots, X_n)$ is an independent sequence of $d$-dimensional Gaussian random vectors with mean 0 and identity covariance matrix, $| \cdot |$ in (7.15) is understood to be the Euclidean norm. Let $b_n = b + \{2\kappa \log[3m/n(1-n/m)]\}^{1/2}$. An approximation for the false positive probability of (7.14) for various choices of $Z_{j,n}$ is as follows:

$$
\mathbb{P}\left\{ \max_{0 \leq j < j+n \leq m} \left( \Sigma^{-1/2} |Z_{j,n}| \right) \geq b \right\} \sim 2 \sum_{n=m_0}^{m_1} (m-n)f_d(b^2_n) \left( \frac{b^4_nq^3_n}{(2n(1-n/m))^2} \right) \nu^2 \left( \frac{b_nq_n}{n(1-n/m)^{1/2}} \right),
$$

(7.16)

where $f_d$ denotes the chi-square probability density function with $d$ degrees of freedom and $q_n = 1 - (d-1)/b^2_n$. The derivation of (7.16) for $d=1$ is similar to that of (2.1) for $d=1$, modified as suggested in the proof of (5) of Zhang et al. (2010) for $d > 1$.

For the likelihood ratio statistic it is easy to see numerically and even to some extent analytically that this probability is very close to additive in the length of the sequence searched. Thus if change-points have been identified, the sum of the false positive probabilities associated with searches for additional change-points in intervals containing no change-points will equal approximately the nominal significance value of the initial search. However, the requirement that change-points be identified in pairs can lead to the detection of a second, spurious change-point in searching an interval where there is only one change-point to be detected.

If for the multiscale statistic one uses the same value of $m$ for searches of subintervals, the false positive probability is super-additive, so the sum of probabilities associated with searches of subintervals containing no change-points is less than the probability associated with the initial search. If one uses the value of $m$ appropriate to the subinterval searched, the probability is sub-additive, so the total false positive probability associated with the
search of a large number of null subintervals is uncontrolled. Hence in our examples, we use a fixed value of \( m \) for searching subintervals. A statistic favoring still longer intervals is the un-normalized statistic

\[
\max_{j,n} m^{-1/2} |(S_{j+n} - S_j - nS_m/m)| \tag{7.17}
\]

suggested by, for example, Aston and Kirch (2012). This statistic has very little power to detect short intervals, but large power to detect intervals that are a substantial fraction, say more than 10% of the entire sequence. However, the sum of false positive probabilities associated with iteratively searching a large number of null intervals is sub-additive, hence uncontrolled. The statistic (7.17) can be studied by the methods described above, but because of its inadequacy for the problems motivating this study, we omit the details here.

**Acknowledgement.** The authors thank Nancy Zhang for several helpful discussions and suggestions. We also thank the two anonymous referees for their detailed comments which led to many improvements. XF was partially supported by NUS grant R-155-000-158-112, CUHK direct grant 4053234 and a CUHK start-up grant. DS was partially supported by the National Science Foundation.

**References**

R. J. Adler and J. E. Taylor (2007). *Random Fields and Geometry* Springer-Verlag, New York-Heidelberg-Berlin.

J. A. D. Aston and C. Kirch (2012). Evaluating stationarity via change-point alternatives with applications to FMRI data. *Ann. Appl. Statist.* **6**, 1906–1948.

H.-P. Chan and Hao Chen (2017). Multi-sequence segmentation via score and higher-criticism tests. arXiv:1706.07586v1.

G. A. Churchill (1989). Stochastic models for heterogeneous DNA sequences. *Bull. Math. Biol.* **51**, 79–94.

P. Diaconis and D. A. Freedman (1988). Conditional limit theorems for exponential families and finite versions of de Finetti’s theorem. *J. Theoret. Probab.* **1**, 381–410.

C. Du, C. L. M. Kao and S. C. Kou (2016). Stepwise signal extraction via marginal likelihood. *J. Amer. Statist. Assoc.* **111**, 314–330.

L. Dümbgen, V. G. Spokoiny (2001). Multiscale testing of qualitative hypotheses *Ann. Statist.* **29**, 124-152.

E. Elhaik, D. Graur and K. Josić (2010) Comparative testing of DNA segmentation algorithms using benchmark simulations, *Mol. Bio. Evol.* **27** 1015-1024.

K. Frick, A. Munk and H. Sieling (2014). Multiscale change point inference. With 32 discussions by 47 authors and a rejoinder by the authors. *J. R. Stat. Soc. Ser. B. Stat. Methodol.* **76**, 495–580.
P. Fryzlewicz (2014). Wild binary segmentation for multiple change-point detection. \textit{Ann. Statist.} \textbf{42}, 2243–2281.

B. James, K. L. James and D. O. Siegmund (1988). Conditional boundary crossing probabilities, with applications to change-point problems. \textit{Ann. Statist.} \textbf{16}, 825–839.

W. R. Lai, M. D. Johnson, R. Kucherlapati and P. J. Park (2005). Comparative analysis of algorithms for identifying amplifications and deletions in array CGH data. \textit{Bioinformatics} \textbf{21}, 3763–3770.

Y.S. Niu and H. Zhang (2012). The screening and ranking algorithm to detect DNA copy number variations. \textit{Ann. Appl. Statist.} \textbf{6}, 1306–1326.

A. B. Olshen, E. S. Venkatraman, R. Lucito and M. Wigler (2004). Circular binary segmentation for the analysis of array-based DNA copy number data. \textit{Biostatistics} \textbf{5}, 557–572.

F. Picard, S. Robin, M. Lavielle, C. Vaisse and J. J. Daudin (2005) A statistical approach for array CGH data analysis. \textit{BMC Bioinformatics} \textbf{6}, 27.

J. R. Pollack, C. M. Perou, A. A. Alizadeh, M. B. Eisen, A. Pergamenschikov, C. F. Williams, S. S. Jeffrey, D. Botstein, and P. O. Brown (1999). Genome-wide analysis of DNA copy-number changes using cDNA microarrays, \textit{Nat. Genet.} \textbf{23}, 41–46.

J. R. Pollack, T. Sorlie, C. M. Perou, C. A. Rees, S. S. Jeffrey, P. E. Lonning, R. Tibshirani, D. Botstein, A. L. Berresen-Dale, and P. O. Brown (2002). Microarray analysis reveals a major direct role of DNA copy number alteration in the transcriptional program of human breast tumors., \textit{Proc. Natl. Acad. Sci. USA} \textbf{99}, 12963–12968.

D. O. Siegmund (1985). \textit{Sequential analysis: Tests and confidence intervals}. Springer, New York.

D. O. Siegmund (1998a). Approximate tail probabilities for the maxima of some random fields. \textit{Ann. Probab.} \textbf{16}, 487–501.

D. O. Siegmund (1988b). Confidence sets in change–point problems. \textit{Internat. Statist. Rev.} \textbf{56}, 31–48.

D. O. Siegmund and B. Yakir (2007). \textit{The Statistics of Gene Mapping}. Springer, New York.

A. M. Snijders, J. Fridlyand, D. A. Mans, R. Segraves, A. N. Jain, D. Pinkel, and D. G. Albertson (2003). Shaping of tumor and drug-resistant genomes by instability and selection. \textit{Oncogene} \textbf{22}, 4370–4379.

I. P. Tu and D. O. Siegmund (1999). The maximum of a function of a Markov chain and application to linkage analysis. \textit{Adv. in Appl. Probab.} \textbf{31}, 510–531.

L. Vostrikova (1981). Detecting ‘disorder’ in multidimensional random processes. \textit{Soviet Math. Dokl.} \textbf{24}, 55–59.

B. Yakir (2013). \textit{Extremes in random fields : a theory and its applications}. Wiley, United Kingdom.

K. J. Worsley (1986). Confidence regions and tests for a change-point in a sequence of exponential family random variables. \textit{Biometrika} \textbf{73}, 91–104.

N. R. Zhang and D. O. Siegmund (2007). A modified Bayes information criterion with applications to the analysis of comparative genomic hybridization data \textit{Biometrics} \textbf{63}, 22–32.
N. R. Zhang, D. O. Siegmund, H. Ji and J. Z. Li (2010). Detecting simultaneous changepoints in multiple sequences. With supplementary data available online. *Biometrika* **97**, 631–645.

N. R. Zhang, B. Yakir, Li C. Xia, D. O. Siegmund (2016). Scan statistics on poisson random fields with applications in genomics. *Ann. Appl. Statist.* **10**, 726-755.

Y. Zhang and J. Liu (2011). Fast and accurate approximation to significance tests in genome-wide association studies. *J. Amer. Statist. Assoc.* **106**, 846-857.

X. Zhao, C. Li, J. G. Paez, K. Chin, P. A. Jänne, T.-H. Chen, L. Girard, J. Minna, D. Christiani, C. Leo, J. W. Gray, W. R. Sellers, and M. Meyerson (2004). An integrated view of copy number and allelic alterations in the cancer genome using single nucleotide polymorphism arrays *Cancer Res.* **64**, 3060–3071.