Time complexity analysis of recently proposed algorithms for optimal changepoint detection

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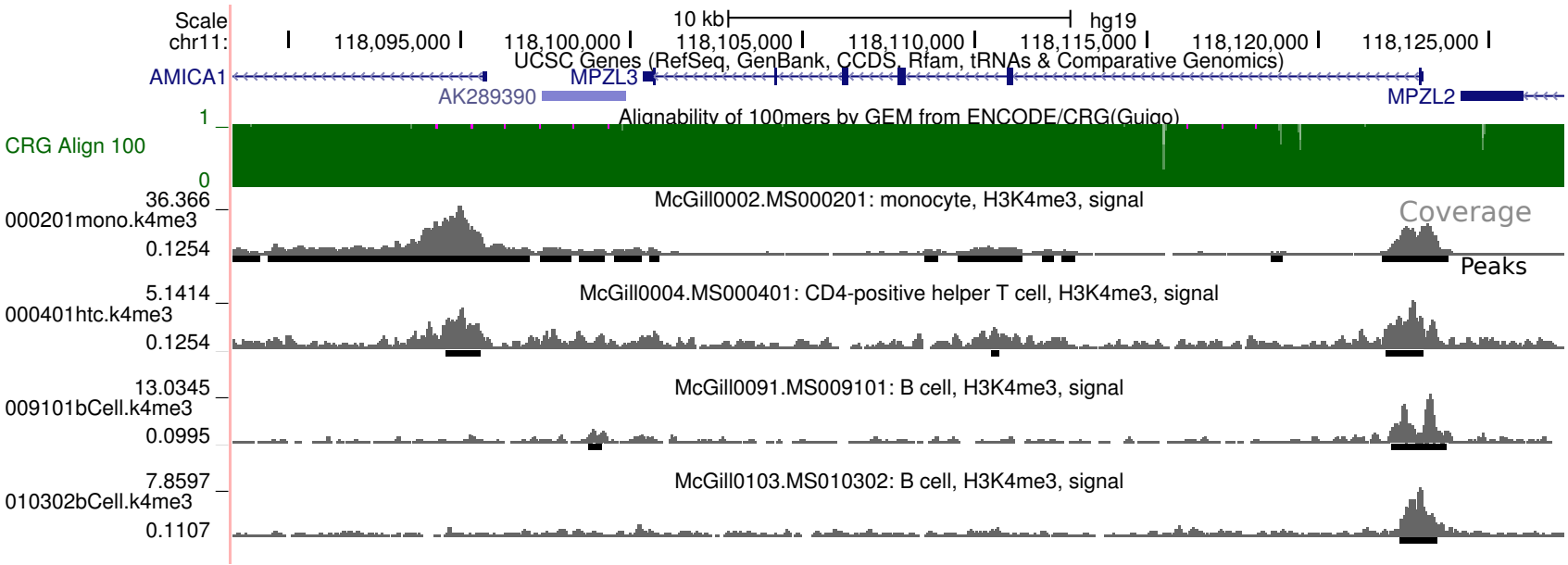
Constrained Dynamic Programming and Supervised Penalty Learning Algorithms for Peak Detection in Genomic Data

Generalized Functional Pruning Optimal Partitioning (GFPOP) for Constrained Changepoint Detection in Genomic Data

Conclusions

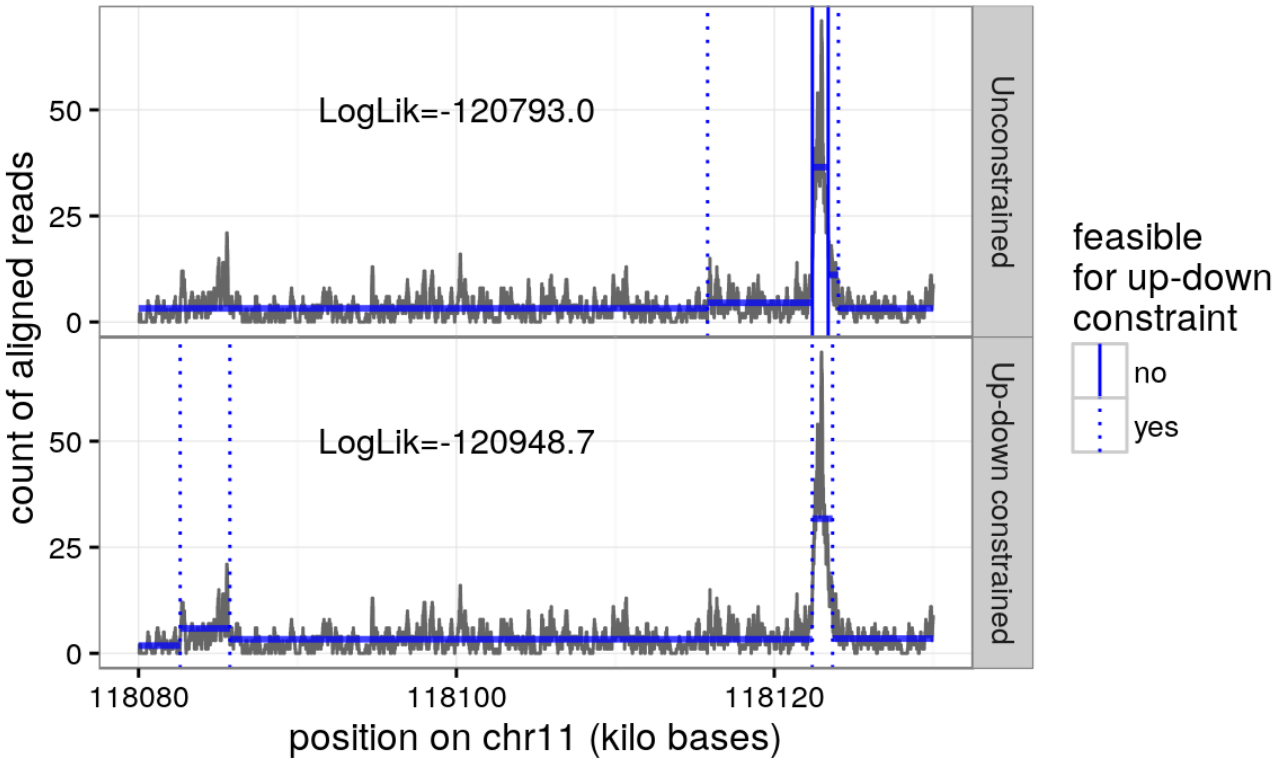
Problem: find peaks in each of several samples



- Grey profiles are noisy aligned read count signals – peaks are genomic locations with protein binding sites.
- Black bars are peaks called by MACS2 (Zhang et al, 2008) – many false positives! (black bars where there is only noise)
- From a machine learning perspective, this could be binary classification (positive=peaks, negative=noise).
- We treat this as a changepoint detection problem with two states.

Citation and new idea

Hocking TD, Rigaill G, Fearnhead P, Bourque G. Constrained Dynamic Programming and Supervised Penalty Learning Algorithms for Peak Detection in Genomic Data. Journal of Machine Learning Research 21(87):1-40, 2020.



New idea: an optimal algorithm for computing best changepoints which alternate up and down (R package PeakSegOptimal).

Comparison to previous work and novelty

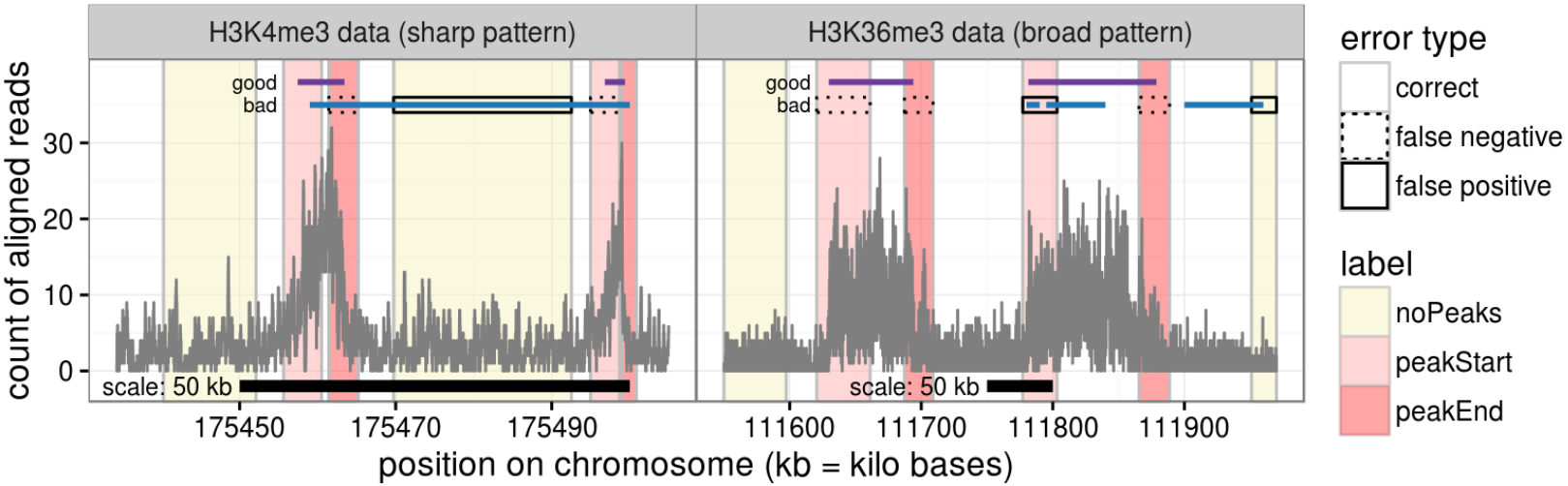
Constraint	No pruning	Functional pruning
None	Dynamic Prog. Algo. (DPA) Optimal, $O(Sn^2)$ time Auger and Lawrence (1989)	Pruned DPA (PDPA) Optimal, $O(Sn \log n)$ time Rigaill (2010); Johnson (2011)
Up-down	Constrained DPA (CDPA) Sub-optimal, $O(Sn^2)$ time Hocking et al. (2015)	Generalized Pruned DPA (GPDPA) Optimal, $O(Sn \log n)$ time **This paper**

$$\underset{\substack{\mathbf{u}\in\mathbb{R}^S \\ 0=t_0<t_1<\cdots<t_{S-1}<t_S=n}}{\text{minimize}} \quad \sum_{s=1}^{S} \sum_{i=1+t_{s-1}}^{t_s} \ell(u_s, z_i)$$

$$\text{subject to} \quad u_{s-1} \leq u_s \ \forall s \in \{2, 4, \dots\},$$
$$u_{s-1} \geq u_s \ \forall s \in \{3, 5, \dots\}.$$

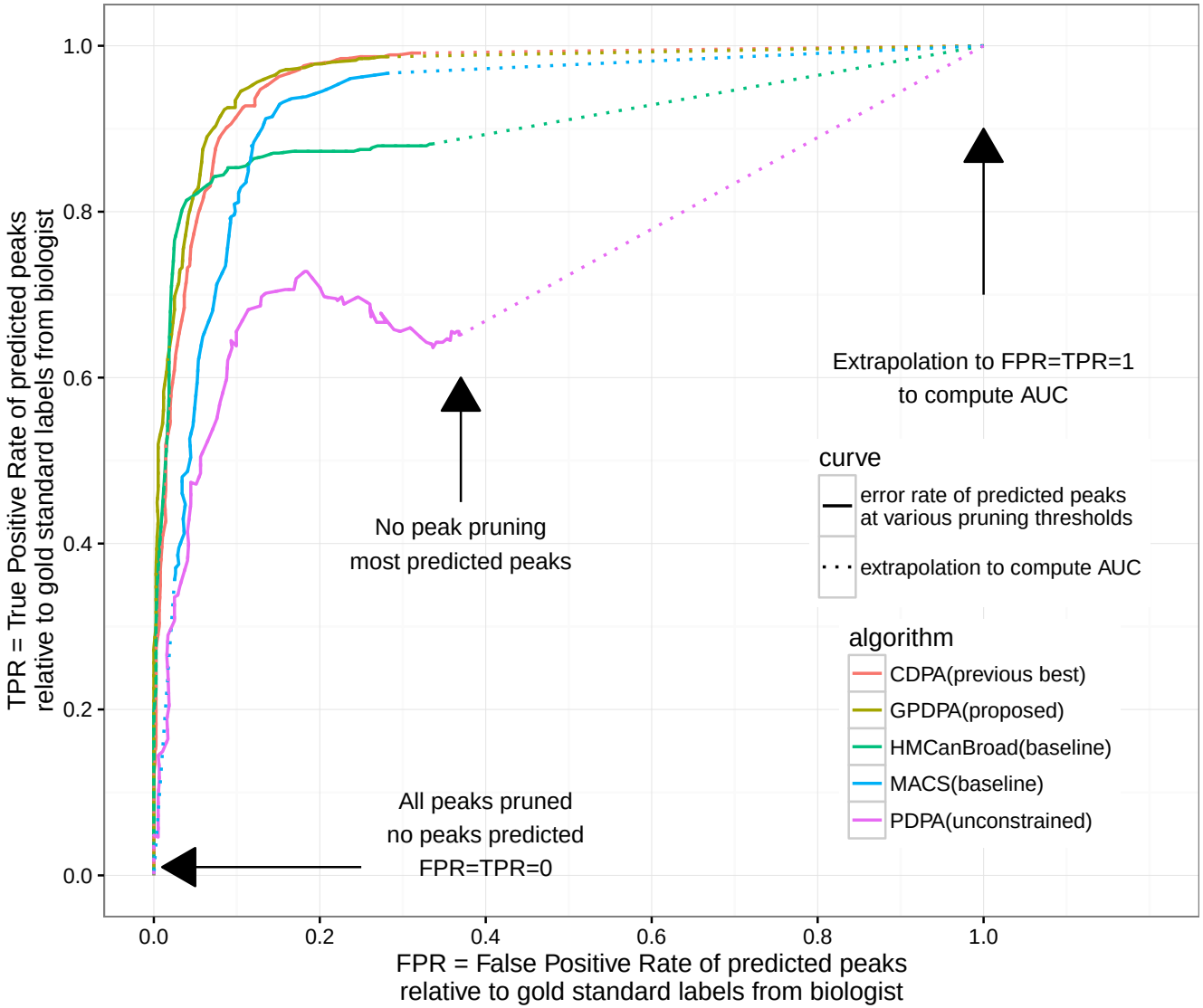
- Let there be a sequence of n data: $z_1, \dots, z_n$.
- One hyper-parameter = number of segments $S \in \{1, 3, \dots\}$.
- Up-down constraints: $P = (S-1)/2$ peaks.
- Discrete/non-convex problem, naively $O(n^S)$ time.
- Main novelty: new fast and optimal algorithm for this constrained problem.

Labeled data setting, learning to predict penalty



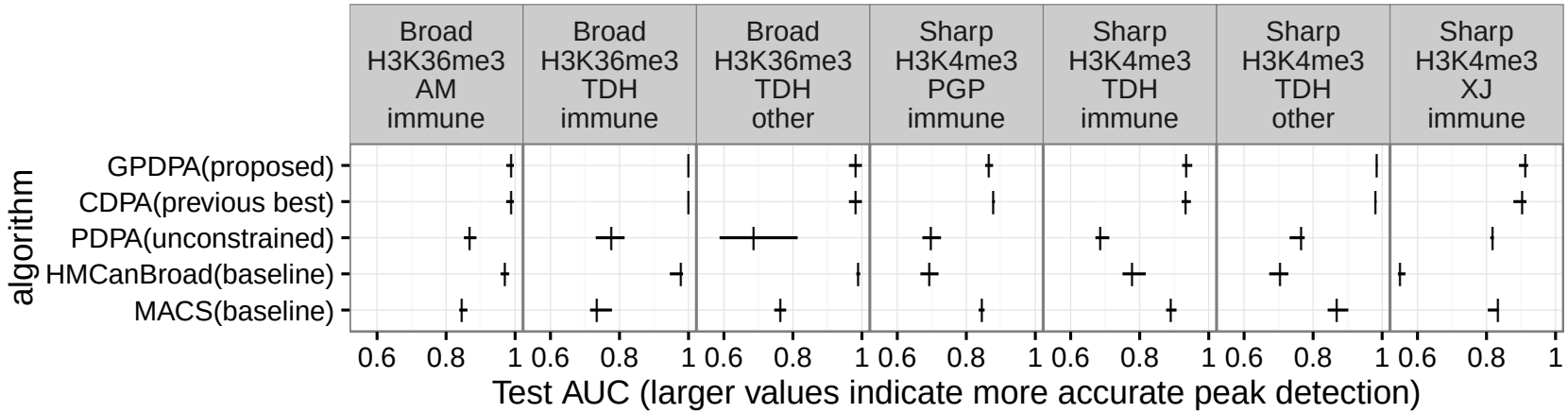
- 2752 expert-labeled sequences (H *et al.*, *Bioinformatics* 2017).
  `https://rcdata.nau.edu/genomic-ml/chip-seq-chunk-db/`
- Split sequences into train and test, learn using labels in train set, then predict peaks on test set.
  - If we have optimal loss L_s for model size s,
  - then for penalty $\lambda \geq 0$ we select the model of size $S^*(\lambda) = \arg\min_s L_s + \lambda s$ (standard linear penalty in statistics).
  - We compute a fixed feature vector x for each sequence, then learn $f(x) = \log \lambda$ to minimize a convex relaxation of label error. (H. *et al.*, ICML'13)

Test ROC curves of predicted peaks



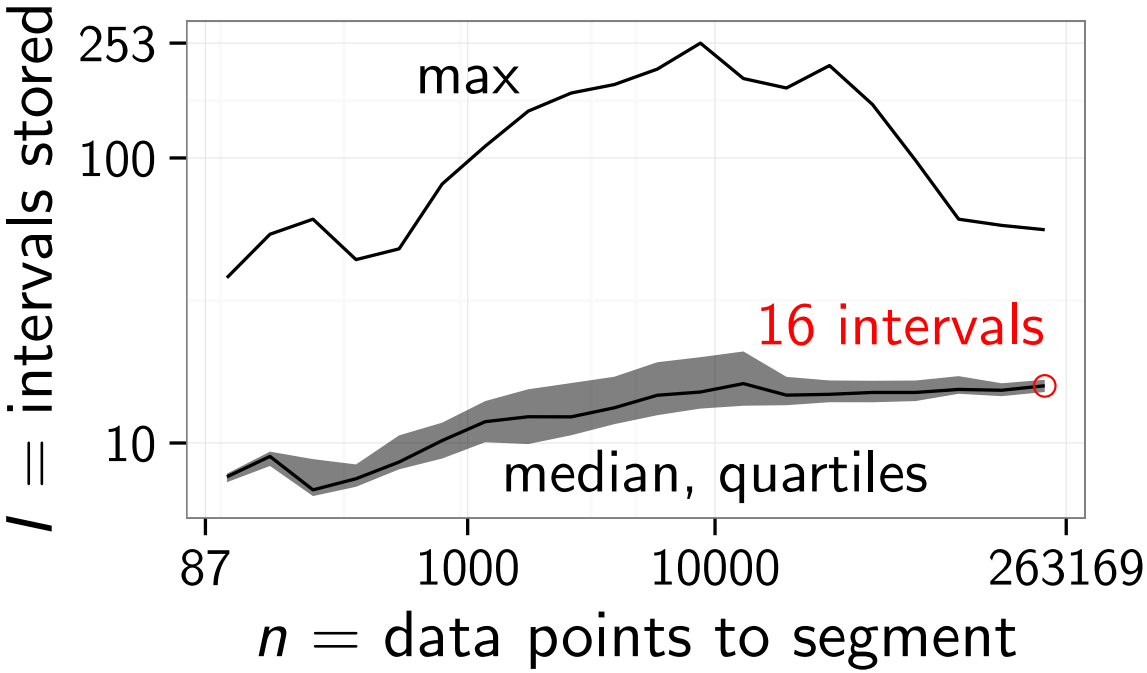
Each point on the ROC curve corresponds to a different penalty λ.

Test AUC of predicted peaks



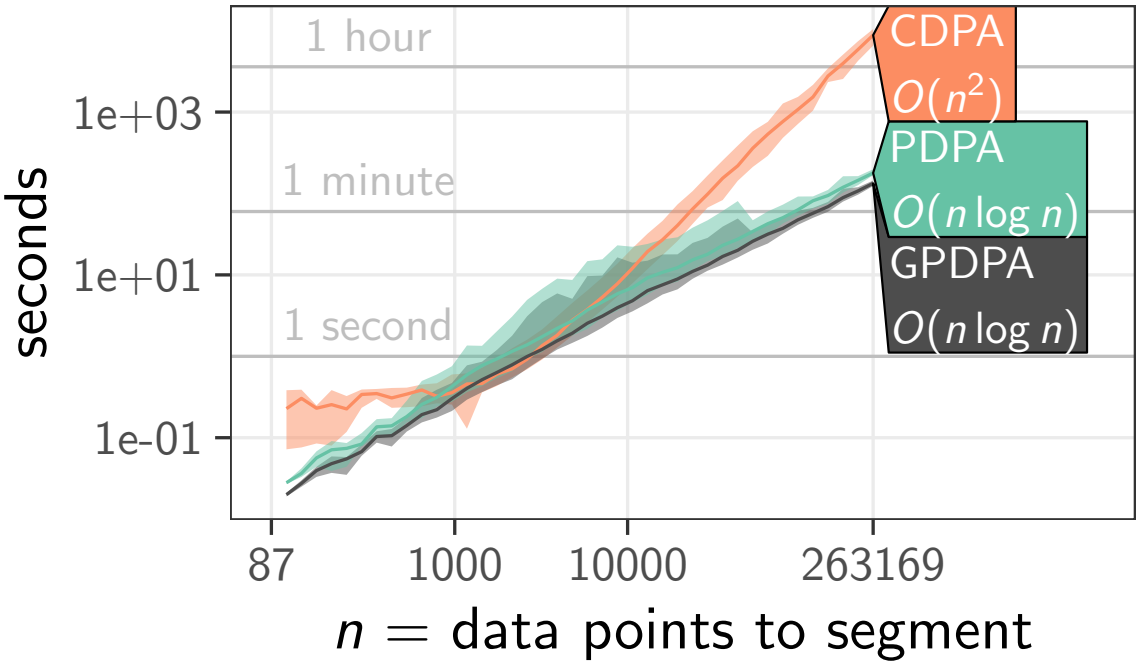
- 4-fold cross-validation: train on 3/4 of labels, test on 1/4.
- All models trained by learning a scalar significance threshold / penalty parameter, which is varied to compute ROC/AUC.
- MACS is highly inaccurate in all data sets.
- HMCanBroad is accurate for broad but not sharp pattern.
- Unconstrained PDPA algorithm not as accurate as up-down constrained algorithms (CDPA, GPDPA).

Time complexity analysis 1 (real genomic ChIP-seq data)



- Dynamic programming algorithm uses functional pruning, which requires storing the cost as a function of the last segment mean.
- This cost function can be computed/stored exactly in terms of several pieces/intervals with different coefficients.
- The algorithm complexity is linear in the number of intervals, and the figure above shows that it is very small, $O(\log n)$, for real data, much smaller than worst case $O(n)$.

Time complexity analysis 2 (real genomic ChIP-seq data)



- Computation time for a fixed number of peaks, 20.
- Proposed GPDPA with up-down constraints is just as fast as previous PDPA with no constraints between adjacent segment means.
- Both are much faster than the CDPA (heuristic/approximate algorithm which enforces up-down constraints).

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Conclusions

Citation and motivation

Hocking TD, Rigaill G, Fearnhead P, Bourque G. Generalized Functional Pruning Optimal Partitioning (GFPOP) for Constrained Changepoint Detection in Genomic Data. Journal of Statistical Software Vol. 101, Issue 10 (2022).

- Previous algorithm computes best models with $1, \ldots, S$ segments for N data in $O(SN \log N)$ time.
- Accurate/fast for relatively small data sets, $N \approx 10^5$, with relatively small number of segments, $S \approx 10^1$.
- But in real data, number of segments grows with number of data (larger data sequences have more peaks).
- For example, largest contig in human genome, $N \approx 10^7$ (ten million data) and $S \approx 10^3$ (thousands of segments), we do not need models with small number of segments/peaks.
- Main novelty: a new optimal algorithm, GFPOP, and an efficient disk-based implementation (R package PeakSegDisk), which computes a single model in $O(N \log N)$ time, even with a large number of segments/peaks.

Previous work on the Segment Neighborhood problem

Constraint	No pruning	Functional pruning
None	Dynamic Prog. Algo. (DPA) Optimal, $O(SN^2)$ time Auger and Lawrence (1989)	Pruned DPA (PDPA) Optimal, $O(SN \log N)$ time Rigaill (2010); Johnson (2011)
Up-down	Constrained DPA (CDPA) Sub-optimal, $O(SN^2)$ time Hocking et al. (2015)	Generalized Pruned DPA (GPDPA) Optimal, $O(SN \log N)$ time Hocking et al. (2020)

- All algorithms solve the **Segment Neighborhood** "constrained" problem: most likely mean m_i for data z_i, subject to the constraint of S segments ($S-1$ changes).

$$\underset{\mathbf{m}\in\mathbb{R}^N}{\text{minimize}} \quad \sum_{i=1}^{N} \ell(m_i, z_i)$$

$$\text{subject to} \quad \sum_{i=1}^{N-1} I[m_i \neq m_{i+1}] = S-1,$$

...up-down constraints on m.

Previous work on the Optimal Partitioning problem

	no pruning	functional pruning
unconstrained	Opt. Part. Algo. exact $O(N^2)$ Jackson et al 2005	FPOP exact $O(N \log N)$ Maidstone et al 2016
up-down constrained		Generalized FPOP exact $O(N \log N)$ **This work**

- All algorithms solve the **Optimal Partitioning** "penalized" problem: most likely mean m_i for data z_i, penalized by a non-negative penalty $\lambda \in \mathbb{R}_+$ for each change:

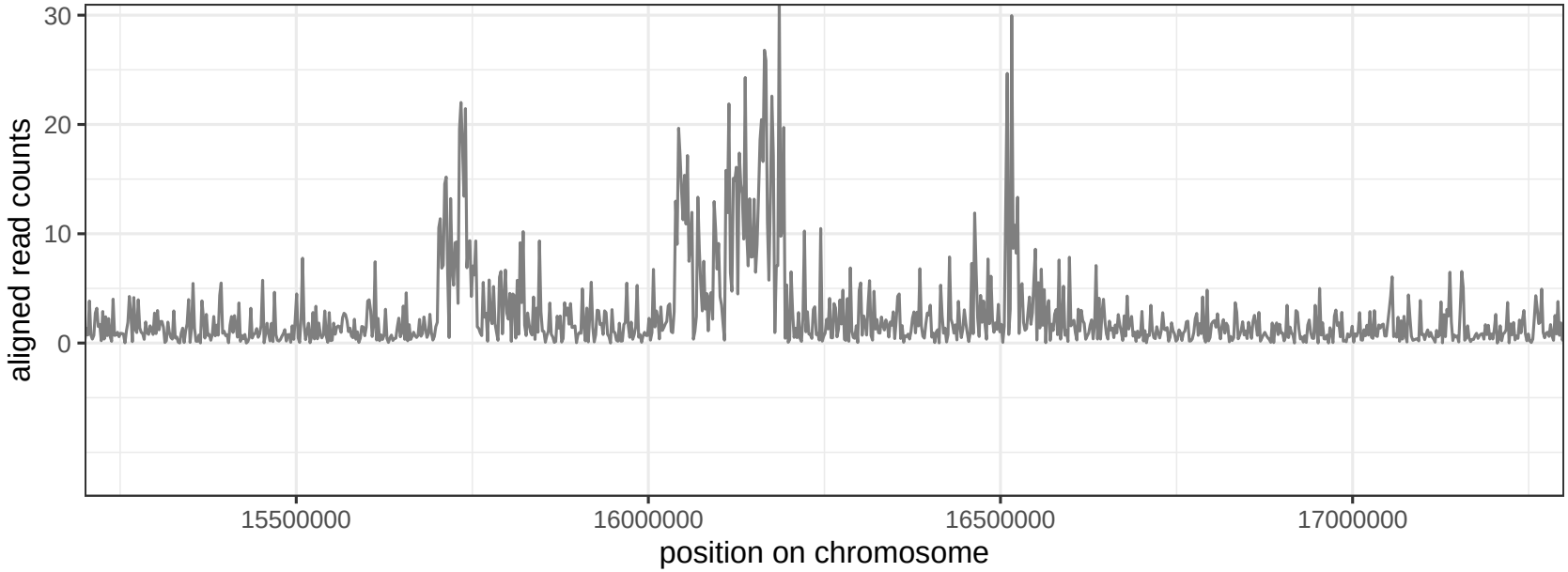
$$\begin{aligned} \underset{\mathbf{m}\in\mathbb{R}^N}{\text{minimize}} \quad & \sum_{i=1}^{N} \ell(m_i, z_i) + \lambda \sum_{i=1}^{N-1} I[m_i \neq m_{i+1}] \\ \text{subject to} \quad & \ldots\text{up-down constraints on } m. \end{aligned}$$

Benchmark of large genomic data sequences

`http://github.com/tdhock/feature-learning-benchmark`

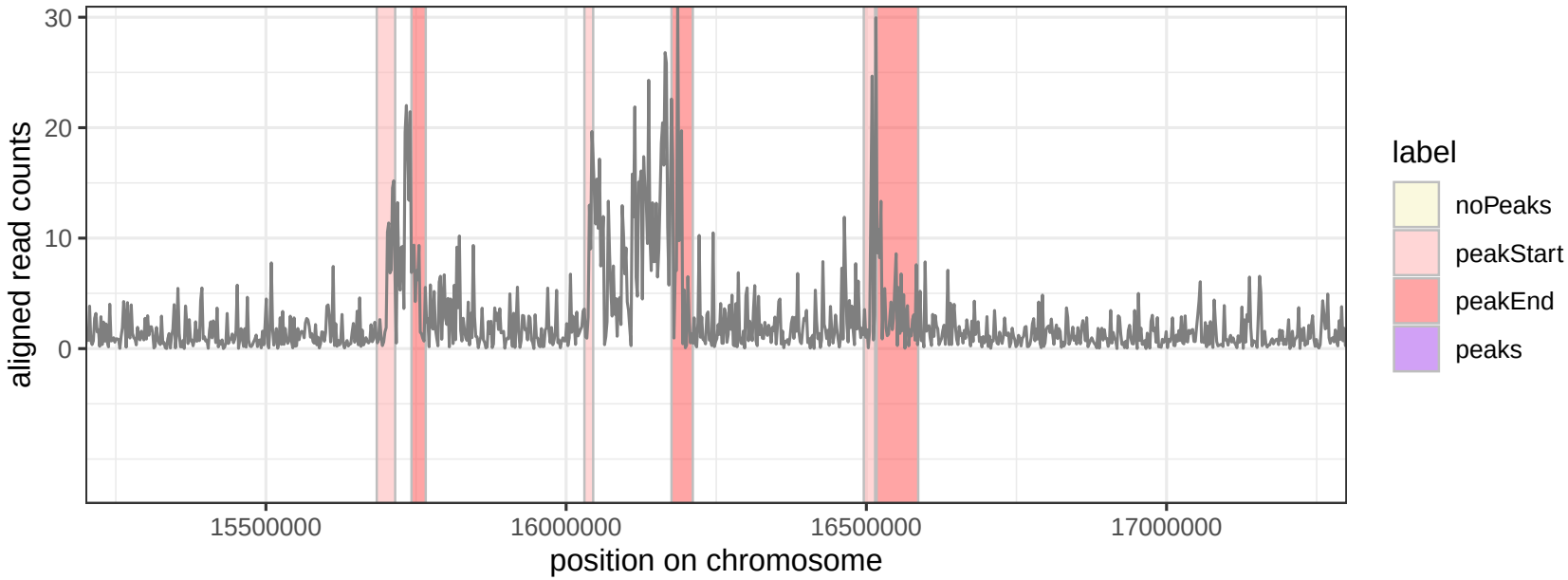
- `chipseq` data set submitted to UCI machine learning repository.
- 4951 data sequences ranging from $N = 10^3$ to $N = 10^7$ (much larger than previous benchmark in terms of number of sequences, and number of data N per sequence).
- Ran GFPOP with penalty $\lambda \in (\log N, N)$, resulting in a range of models with different numbers of peaks, for each data sequence.
- How to determine penalty value(s) most appropriate for a given data sequence?
- Each data set has **labels** from experts which can be used to determine an appropriate number of peaks.

Labels used to determine optimal number of peaks



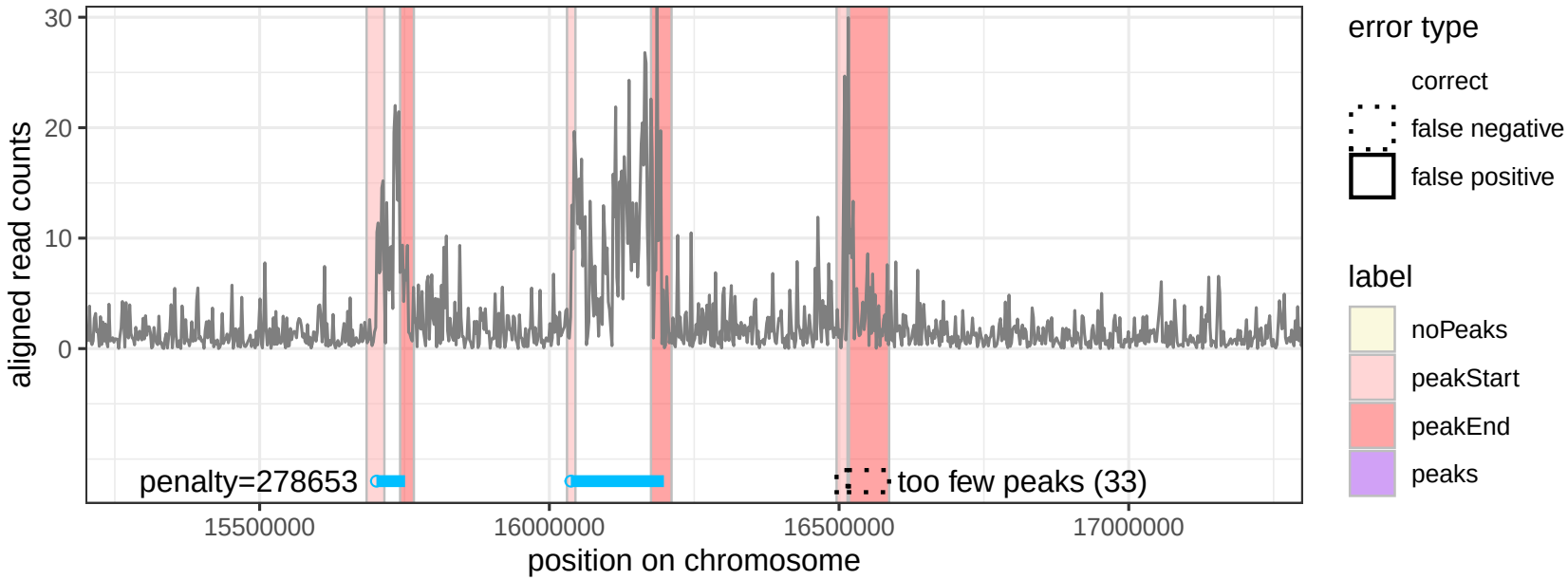
One ChIP-seq data set with $N = 1,254,751$ (only 82,233 shown).

Labels used to determine optimal number of peaks



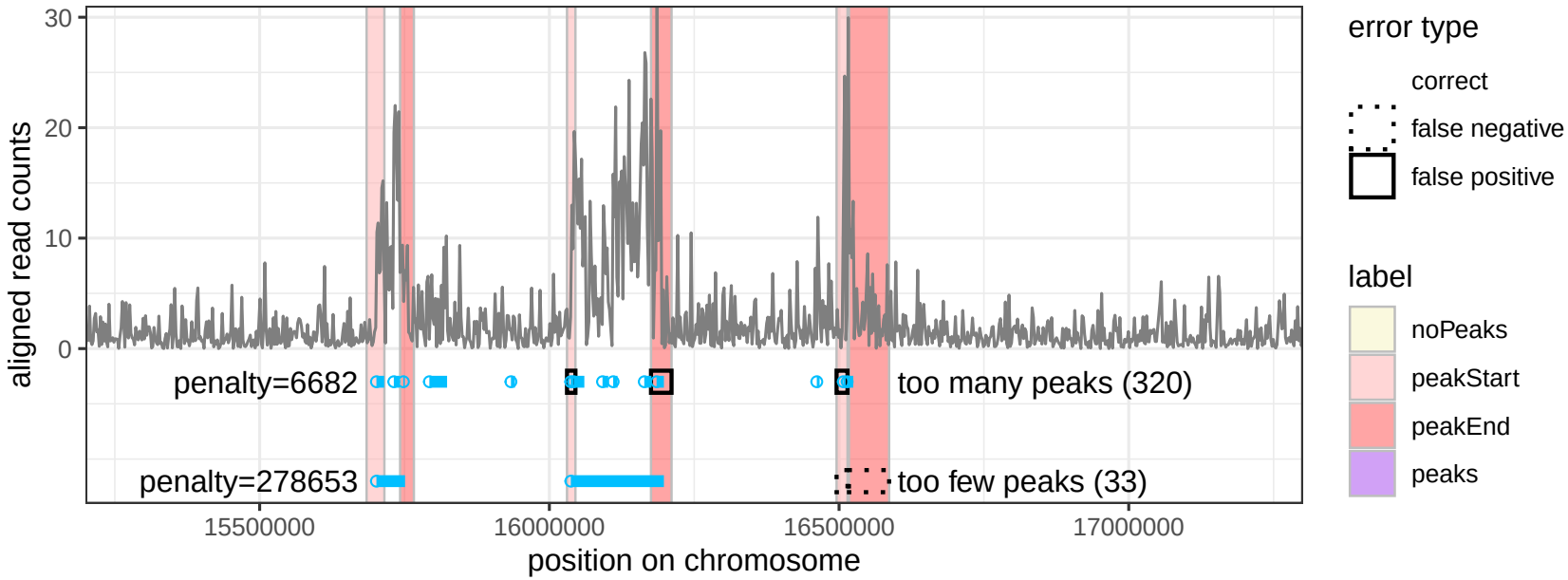
Visually labeled regions (H *et al.*, *Bioinformatics* 2017).

Labels used to determine optimal number of peaks



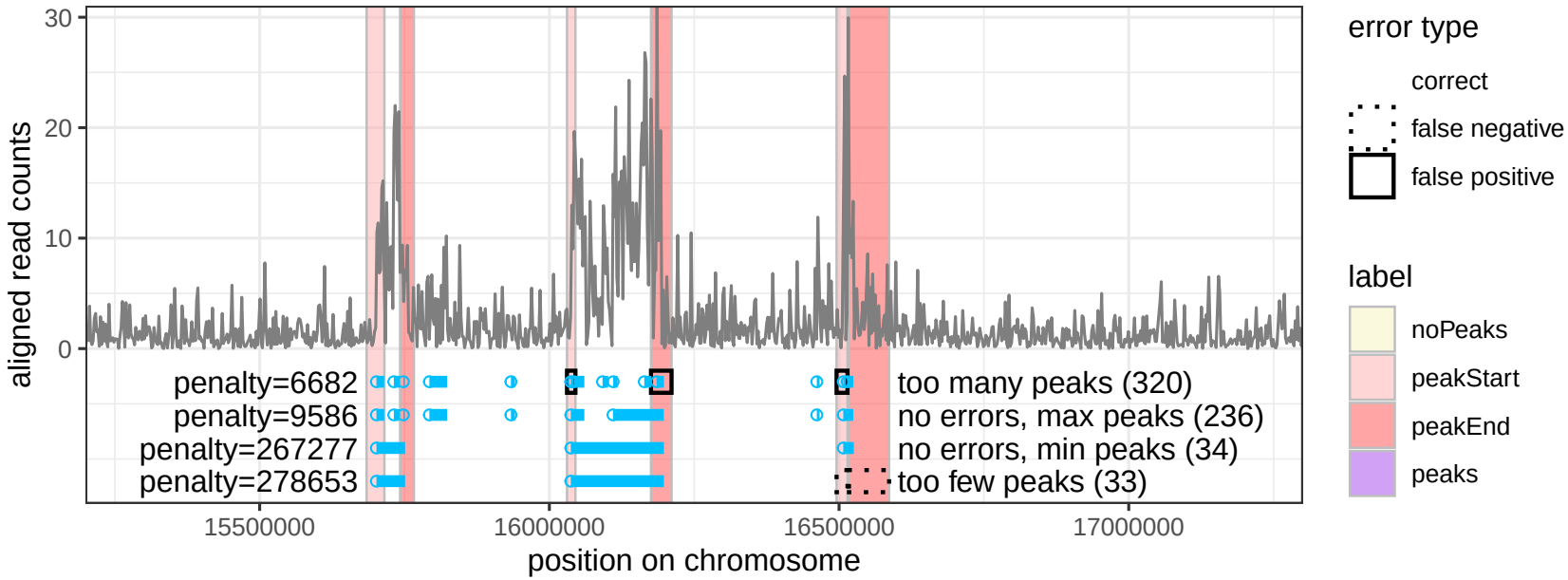
Penalty too large, too few peaks, 2 false negative labels.

Labels used to determine optimal number of peaks



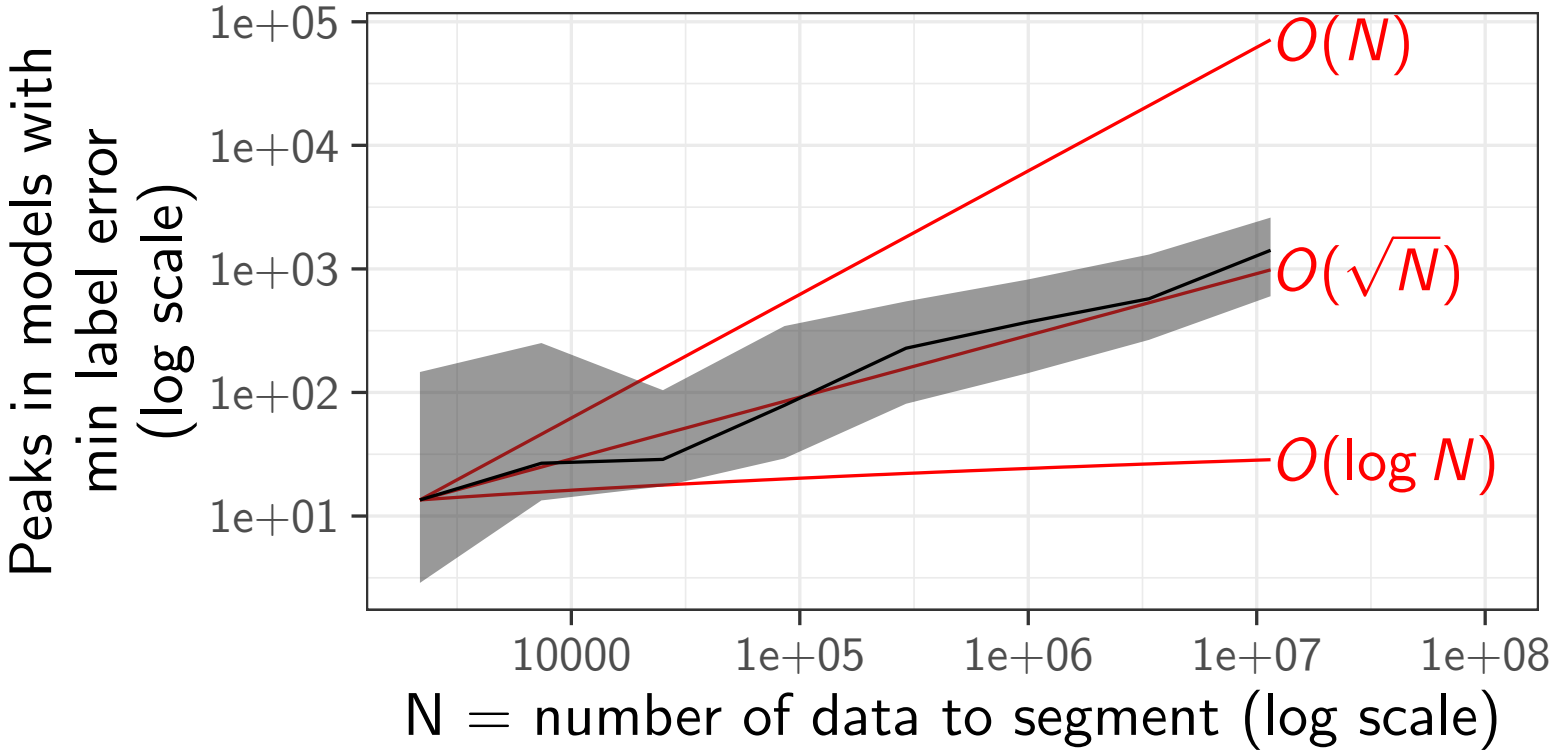
Penalty too small, too many peaks, 3 false positive labels.

Labels used to determine optimal number of peaks



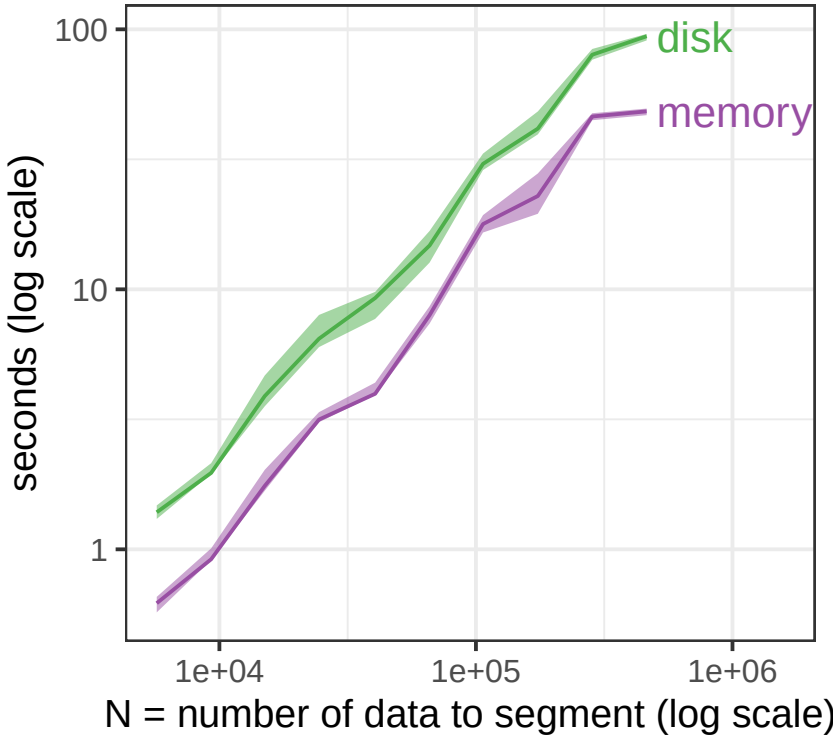
Models with 34–236 peaks have no label errors (midpoint=135).

Segment Neighborhood model too slow for $O(\sqrt{N})$ peaks



- Previous GPDPA: $O(S)$ dynamic programming iterations, each is $O(N \log N)$ time/space.
- If we want $S = O(\sqrt{N})$ segments then the algorithm is $O(N\sqrt{N} \log N)$ time/space – too much for large data.
- For example $N = 10^7$ data. Each $O(N \log N)$ DP iteration takes 1 hour, 80 GB. Overall if we want $S = O(\sqrt{N}) = 2828$ segments we need 220 TB of storage and 17 weeks!

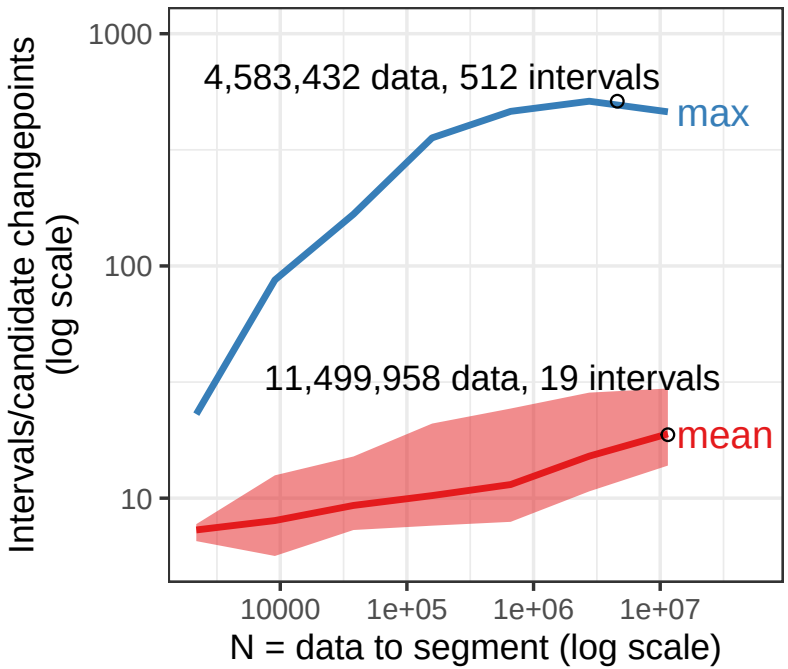
Implementation stores cost functions on disk



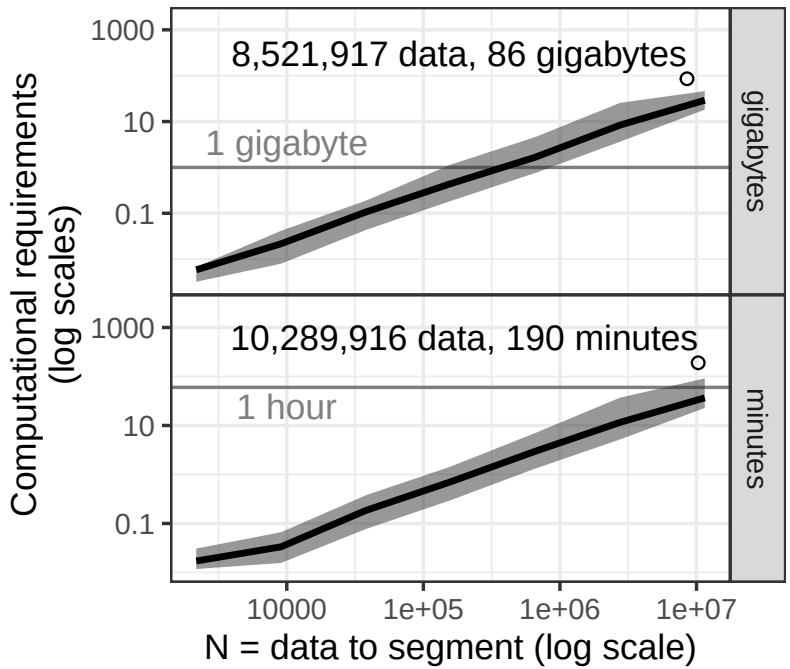
- Proposed GFPOP (Generalized FPOP) algorithm implemented using disk-based storage in R package `PeakSegDisk`.
- Disk storage is only a constant factor slower than memory.
- Both are $O(N \log N)$ time.
- Memory implementation: $O(N \log N)$ memory. (too big)
- Disk implementation: $O(\log N)$ memory (< 1GB), $O(N \log N)$ disk.

Time/space to solve one penalty is $O(N \log N)$

Total time/space $= O(NI)$ where I is the number of intervals (candidate changepoints) stored in every optimal cost function.



$I = O(\log N)$ intervals.



Overall $O(N \log N)$ complexity.

- So we can efficiently compute the best model for a given penalty λ.
- But how to compute model with $O(\sqrt{N})$ peaks?

Sequential search algorithm using GFPOP to compute most likely model with at most P^* peaks

1: Input: data $\mathbf{z} \in \mathbb{R}^N$, target peaks P^*.
2: $\overline{L}, \overline{p} \leftarrow \text{GFPOP}(\mathbf{z}, \lambda = 0)$ // max peak model
3: $\underline{L}, \underline{p} \leftarrow \text{GFPOP}(\mathbf{z}, \lambda = \infty)$ // 0 peak model
4: While $\underline{p} \neq P^*$ and $\overline{p} \neq P^*$:
5: $\quad \lambda = (\overline{L} - \underline{L})/(\underline{p} - \overline{p})$
6: $\quad L_{\text{new}}, p_{\text{new}} \leftarrow \text{GFPOP}(\mathbf{z}, \lambda)$
7: $\quad$ If $p_{\text{new}} \in \{\underline{p}, \overline{p}\}$: return model with $\underline{p}$ peaks.
8: $\quad$ If $p_{\text{new}} < P^*$: $\underline{p} \leftarrow p_{\text{new}}$
9: $\quad$ Else: $\overline{p} \leftarrow p_{\text{new}}$
10: If $\underline{p} = P^*$: return model with $\underline{p}$ peaks.
11: Else: return model with $\overline{p}$ peaks.

- New penalty λ guaranteed to make progress toward P^* peaks.
- Time complexity depends on number of iterations of while loop (number of calls to GFPOP sub-routine).

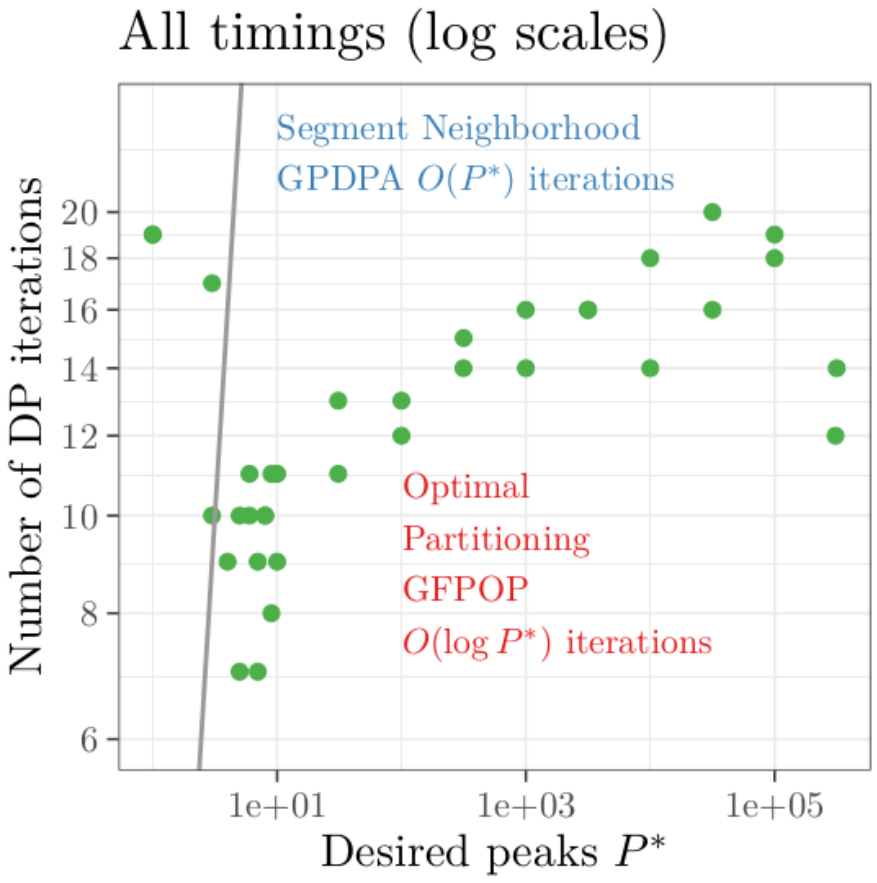
Example run of sequential search algorithm

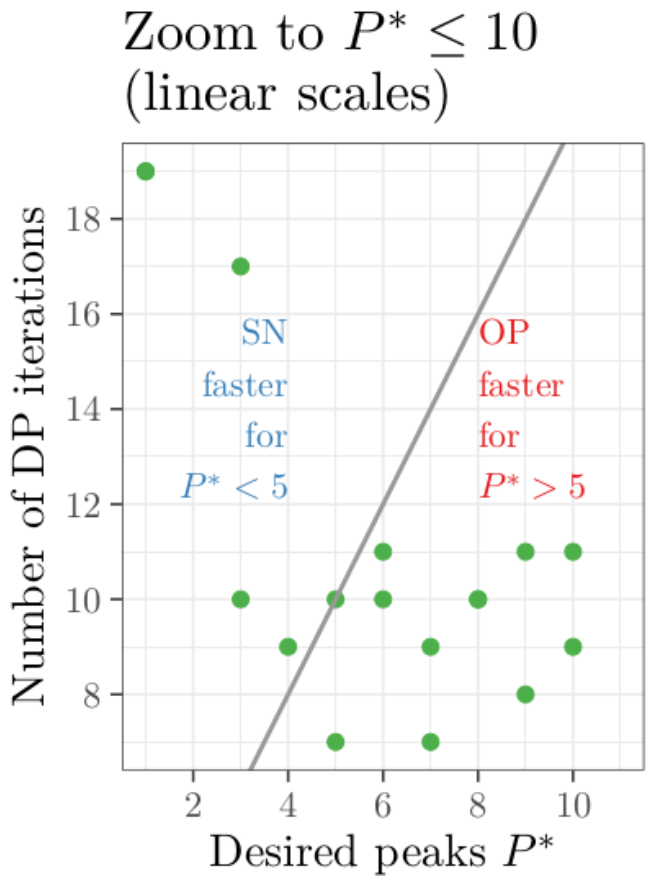
- One data set with $P^* = 93$ peaks and $N = 146,186$ data.
- 12 DP iterations much fewer than $93 \times 2 = 186$ required for previous GPDPA (Segment Neighborhood problem).

iteration	$\underline{p}$	$\overline{p}$	λ	p_{new}	L_{new}
0			∞	0	14239212
1			0	68752	-2570319
2	0	68752	244.4952	4361	1980119
3	0	4361	2811.0738	188	3676671
4	0	188	56183.7271	55	5330310
5	55	188	12433.3766	98	4108354
6	55	98	28417.5941	72	4584042
7	72	98	18295.6895	83	4336773
8	83	98	15227.9249	90	4218815
9	90	98	13807.6282	95	4146172
10	90	95	14528.5052	92	4188881
11	92	95	14236.0863	94	4160179
12	92	94	14350.6622	93	4174480

How large must the model size P^* be for the new algorithm to be faster?

Only $O(\log N)$ runs of GFPOP even for large models





- Experiment with two large data sequences $N \approx 10^7$, varying the number of desired peaks.
- Proposed Optimal Partitioning + sequential search algorithm is faster than previous Segment Neighborhood algorithm, for model sizes $P^* > 5$.

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Conclusions

Conclusion: optimal peak detection for large data

- New algorithms for optimal changepoint detection in peak/background model, with constraints or penalty on number of changes/peaks.
- New R packages with efficient C++ code: PeakSegOptimal, PeakSegDisk.
- Makes it possible to compute an optimal model, with a large number of peaks, in huge genomic data sets, on your laptop.
- Future work: more general graph-based constraints for other data types (not just up-down peak pattern).
- Contact me: toby.hocking@nau.edu
- Thanks!

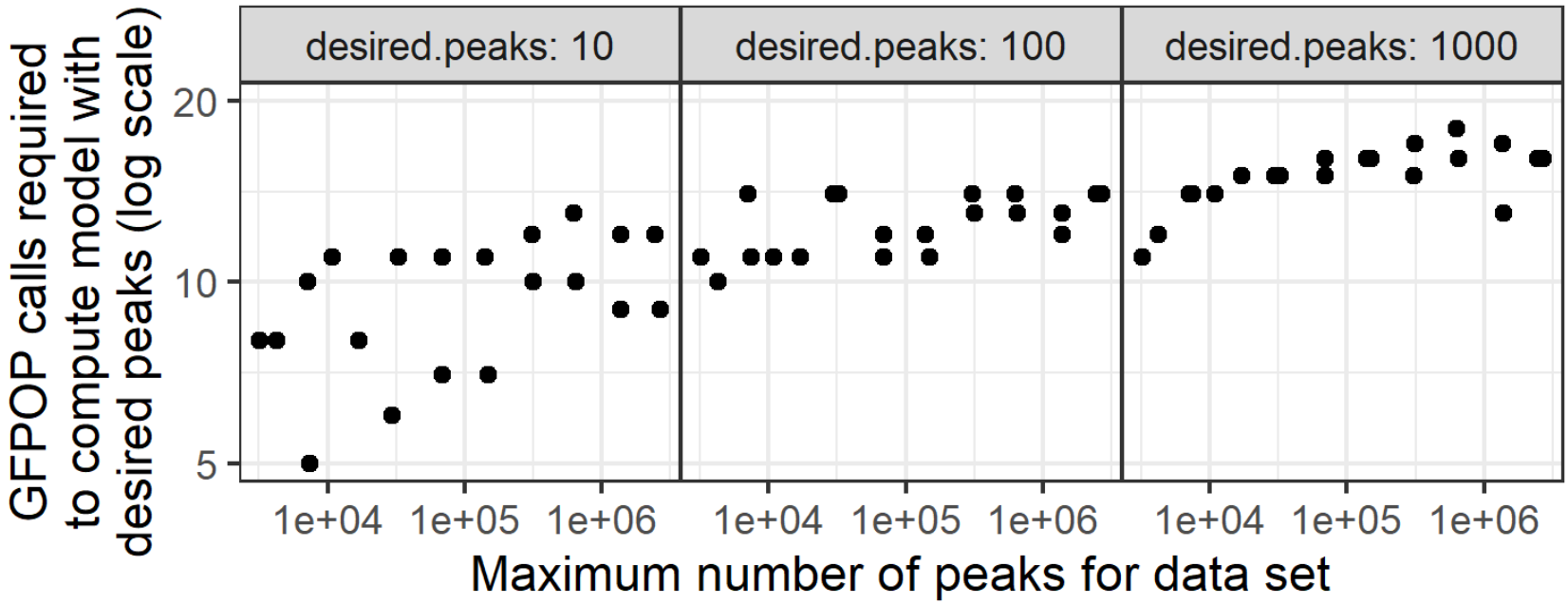
For some data the desired number of peaks does not exist!

One data set with $P^* = 75$ and $N = 66,031$ data.

iteration	$\underline{p}$	$\overline{p}$	λ	p_{new}	L_{new}
1			0	29681	-1495863.85
1			∞	0	1200631.42
2	0	29681	90.85	3445	-1245181.37
3	0	3445	709.96	401	-446632.57
4	0	401	4107.89	51	3105.03
5	51	401	1284.96	168	-230152.31
6	51	168	1993.65	97	-120725.83
7	51	97	2691.98	68	-53946.18
8	68	97	2302.75	81	-86423.80
9	68	81	2498.28	77	-76891.10
10	68	77	2549.44	71	-61722.09
11	71	77	2528.17	74	-69330.62
12	74	77	2520.16	76	-74374.78
13	74	76	2522.08	76	-74374.78

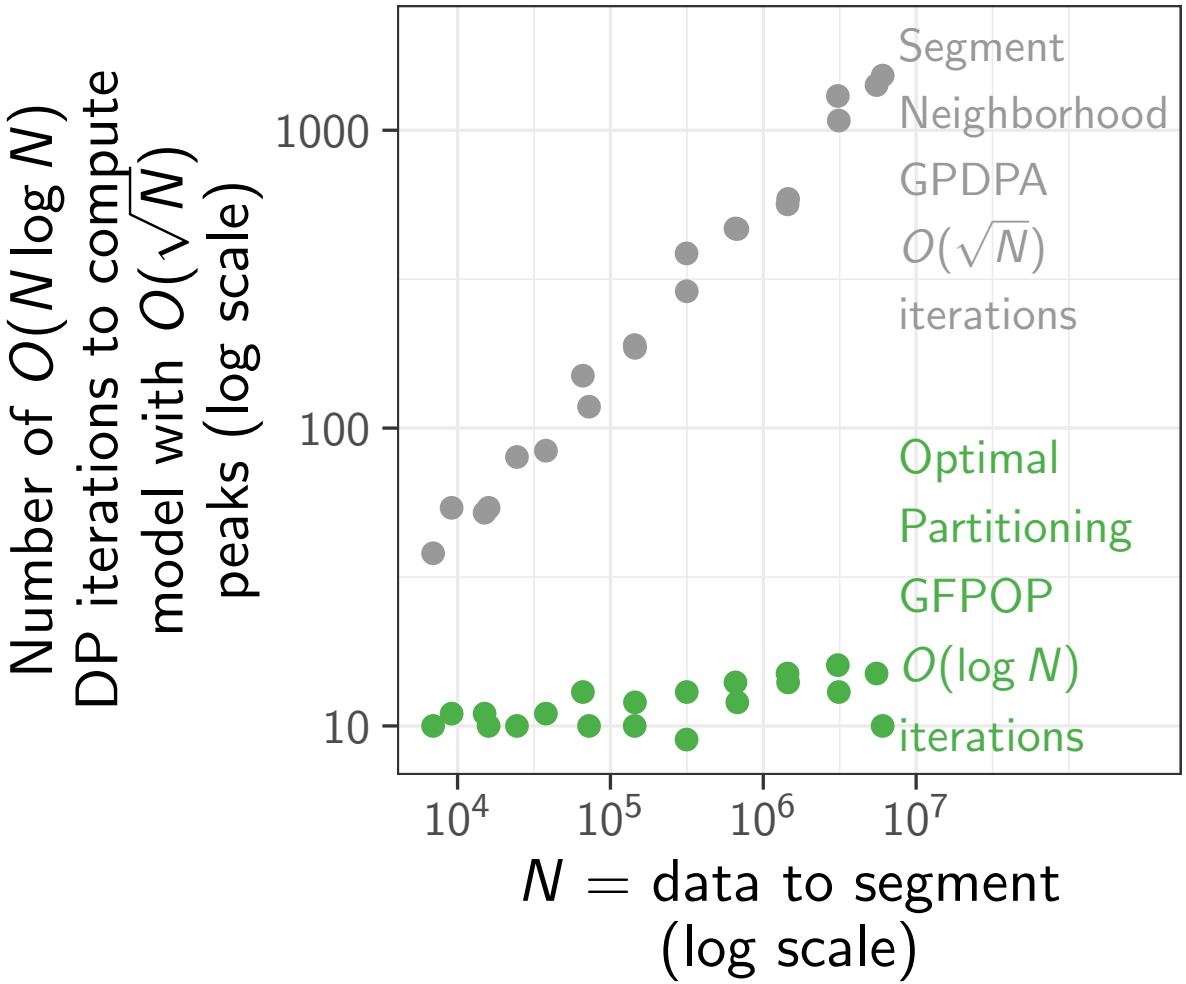
No model exists between $\underline{p} = 74$ and $\overline{p} = 76$, so algo stops and returns the simpler model with 74 peaks.

Number of GFPOP calls increases slowly with maximum number of peaks



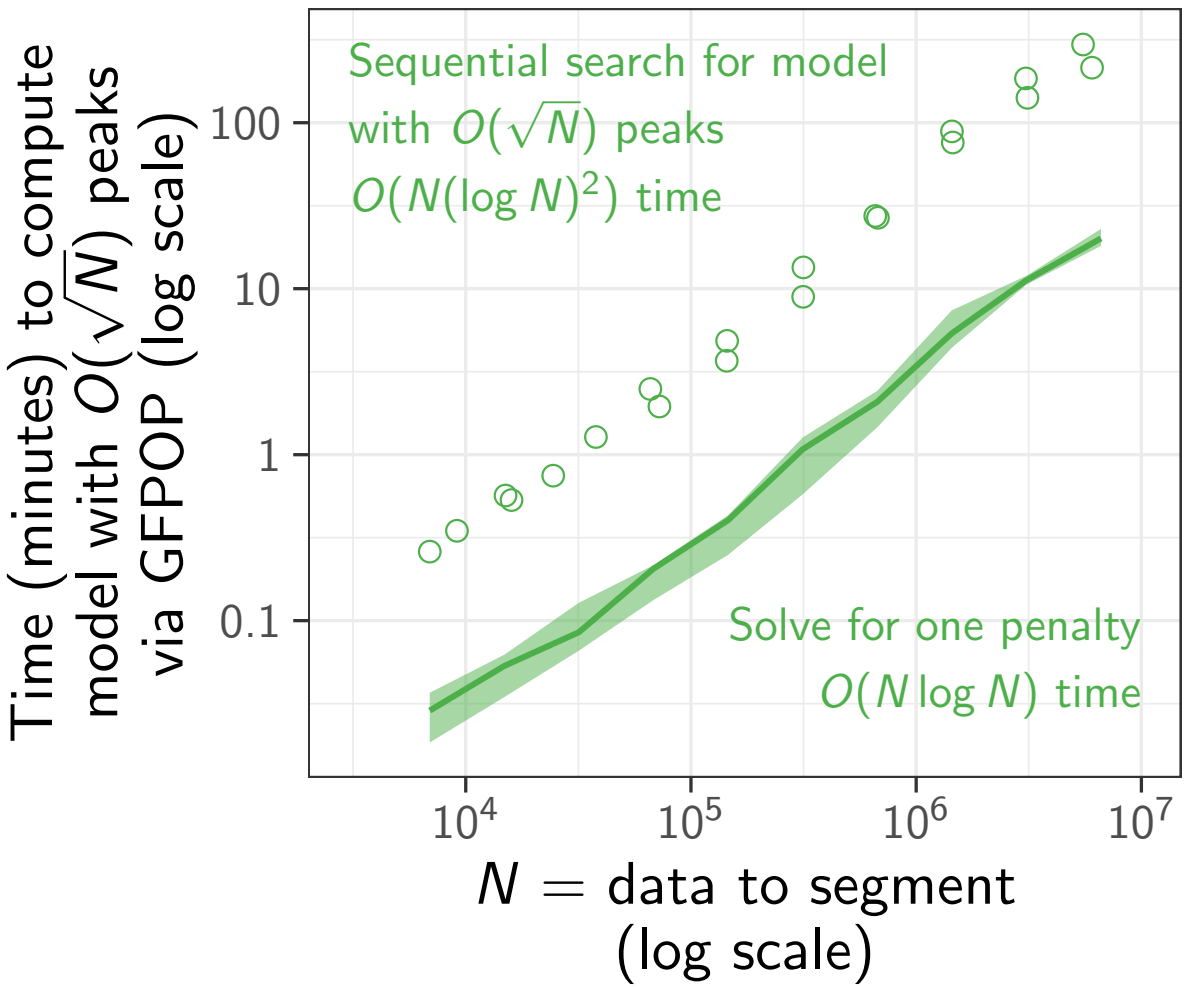
- Run GFPOP with penalty $\lambda = 0$ to determine max number of peaks for each data sequence.
- Run sequential search on each data sequence with desired peaks $P^* \in \{10, 100, 1000\}$.

Only $O(\log N)$ runs of GFPOP to compute $O(\sqrt{N})$ peaks



- Proposed Optimal Partitioning algorithm + sequential search algorithm is much faster than previous Segment Neighborhood algorithm.

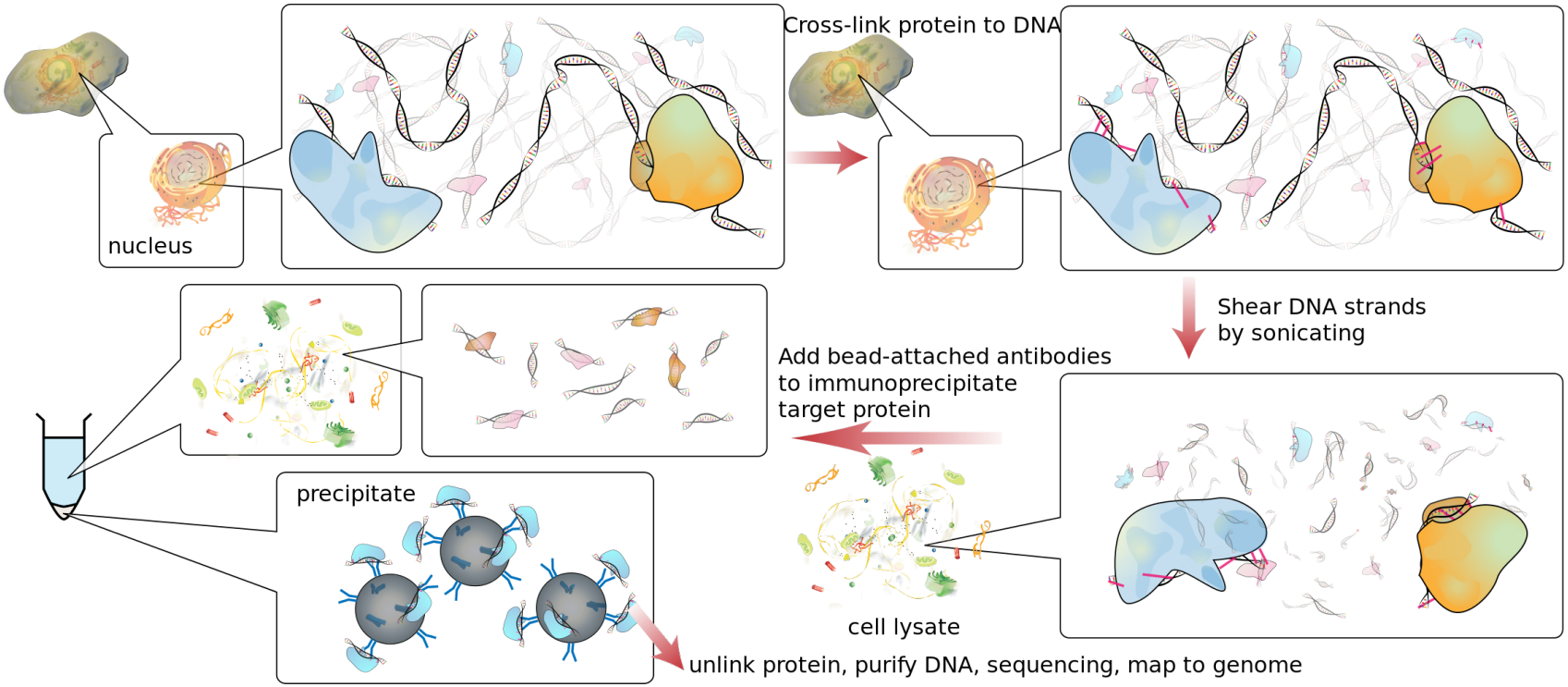
Sequential search only a log factor slower than solving one penalty



For $N = 10^7$ only several hours of computation! (compare with weeks for Segment Neighborhood algorithm)

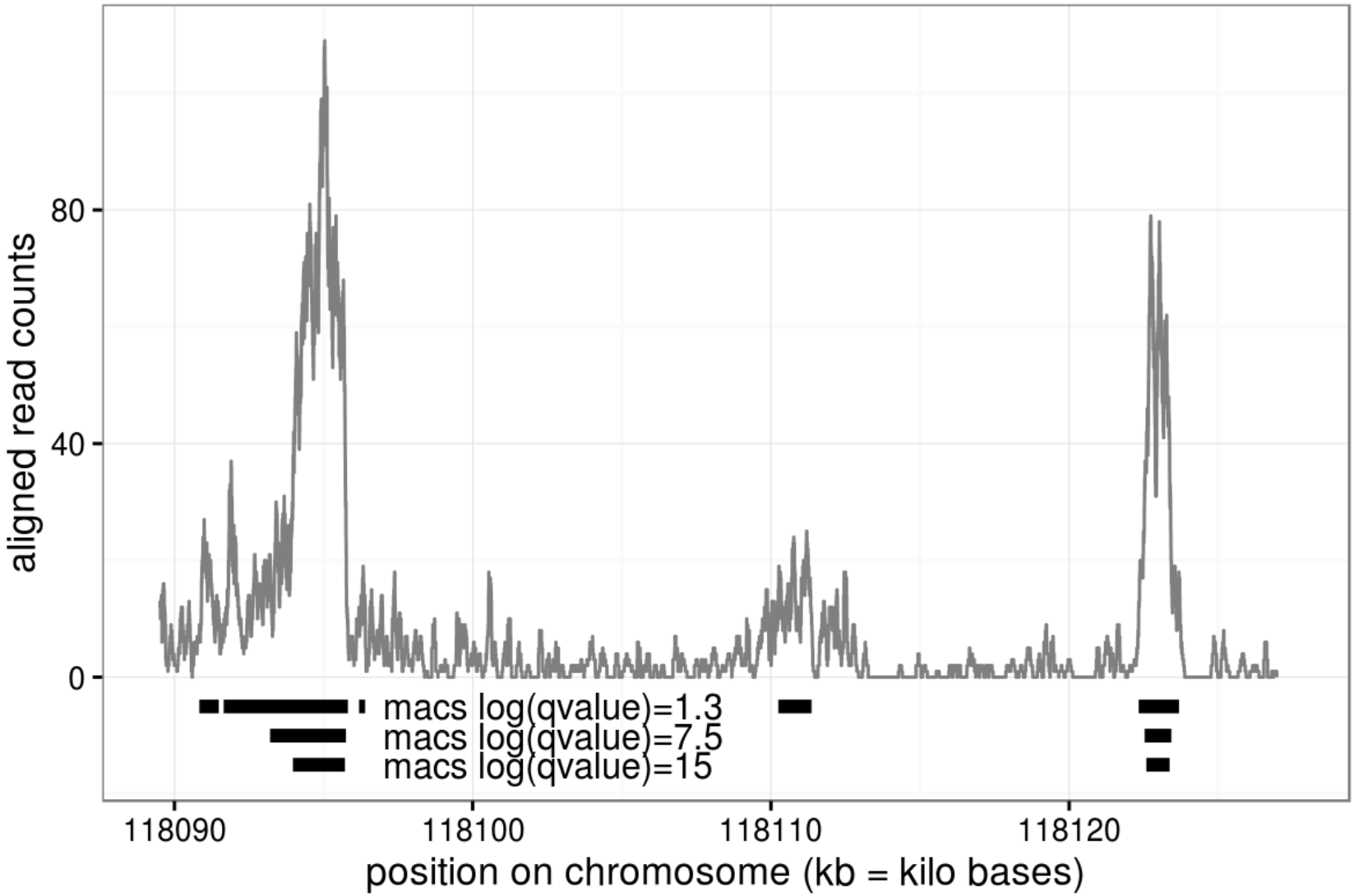
Chromatin immunoprecipitation sequencing (ChIP-seq)

Analysis of DNA-protein interactions.

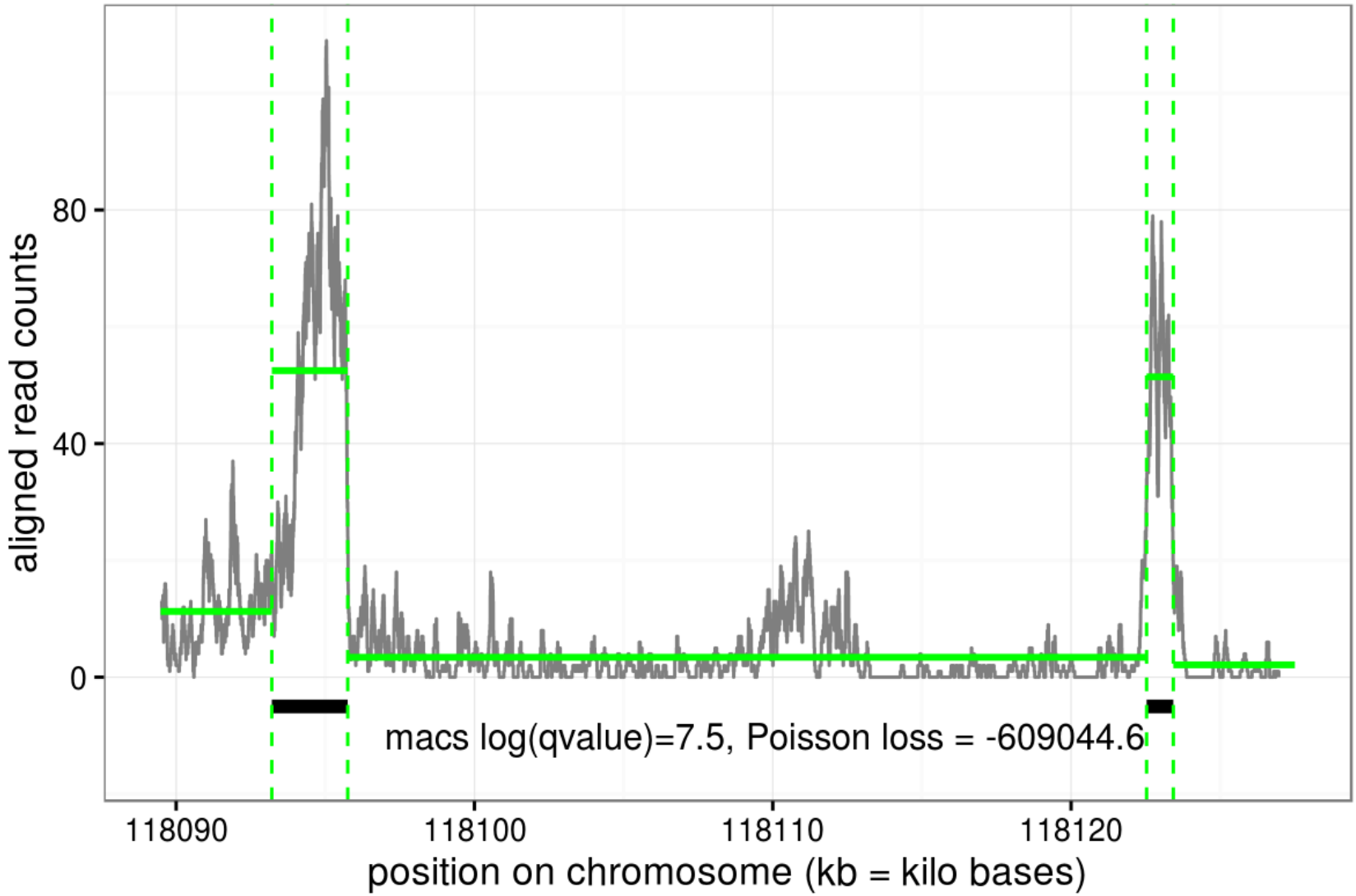


Source: "ChIP-sequencing," Wikipedia.

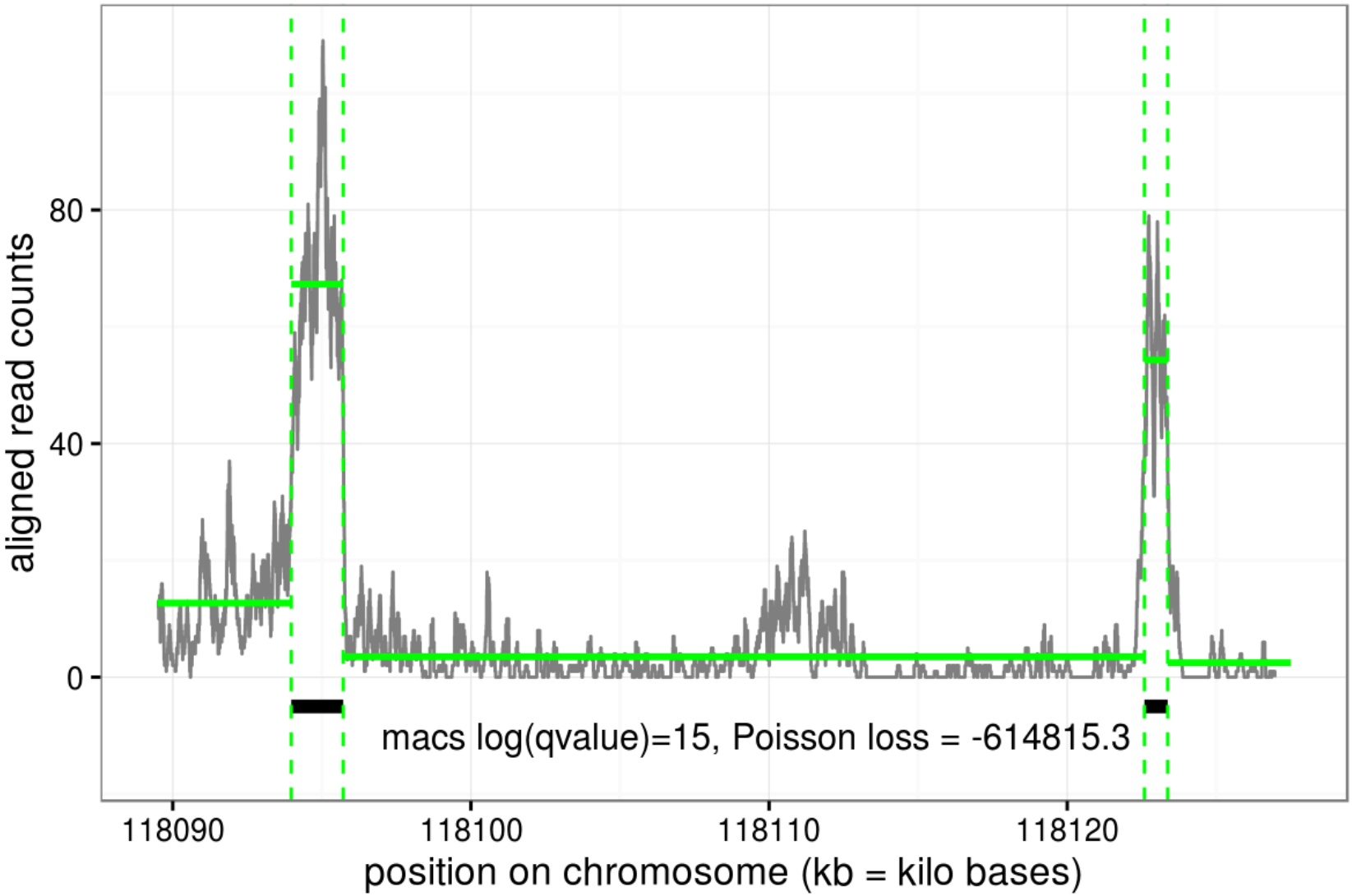
Which macs parameter is best for these data?



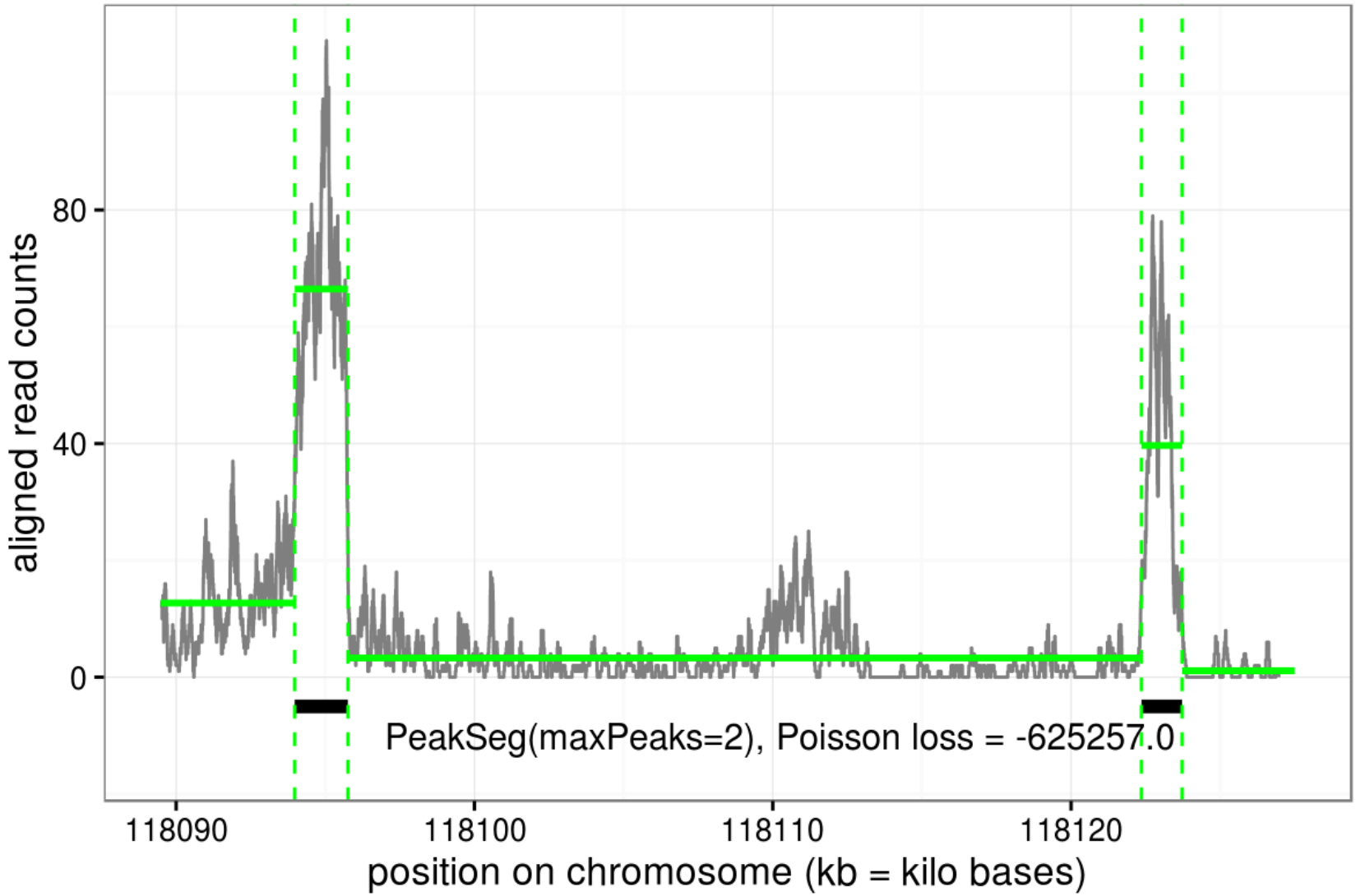
Compute likelihood/loss of piecewise constant model



Idea: choose the parameter with a lower loss



PeakSeg: search for the peaks with lowest loss



Simple model with only one parameter (number of peaks).

Statistical model is a piecewise constant Poisson mean

H *et al.*, *ICML* 2015.

- We have n count data $z_1, \ldots, z_n \in \mathbb{Z}_+$.
- Fix the number of segments $S \in \{1, 2, \ldots, n\}$.
- Optimization variables: $S-1$ changepoints $t_1 < \cdots < t_{S-1}$ and S segment means $u_1, \ldots, u_S \in \mathbb{R}_+$.
- Let $0 = t_0 < t_1 < \cdots < t_{S-1} < t_S = n$ be the segment limits.
- Statistical model: for every segment $s \in \{1, \ldots, S\}$, $z_i \overset{\text{iid}}{\sim} \text{Poisson}(u_s)$ for every data point $i \in (t_{s-1}, t_s]$.
- PeakSeg up-down constraint: $u_1 \leq u_2 \geq u_3 \leq u_4 \geq \cdots$
- Want to find means u_s which maximize the Poisson likelihood: $P(Z = z_i | u_s) = u_s^{z_i} e^{-u_s} / (z_i!)$.
- Equivalent to finding means u_s which minimize the Poisson loss: $\ell(u_s, z_i) = u_s - z_i \log u_s$.

Dynamic programming and functional pruning

Classical dynamic programming for optimal partitioning (Jackson et al 2005) computes the vector of optimal loss values up to N data points, $O(N^2)$ time because each DP iteration needs to consider all $O(N)$ possible changepoints and cost values.

$$\mathcal{C}_1 \quad \mathcal{C}_2 \quad \cdots \quad \mathcal{C}_{N-1} \quad \mathcal{C}_N$$

Functional pruning optimal partitioning (Maidstone 2016) computes a vector of loss **functions**, $O(N \log N)$ because each DP iteration only considers $O(\log N)$ candidate changepoints (the others — which will never be optimal — are pruned).

$$C_1(m_1) \quad C_2(m_2) \quad \cdots \quad C_{N-1}(m_{N-1}) \quad C_N(m_N)$$

Contribution of this work: a new algorithm that applies the functional pruning technique to the up-down constrained model.

Constrained optimal partitioning problem

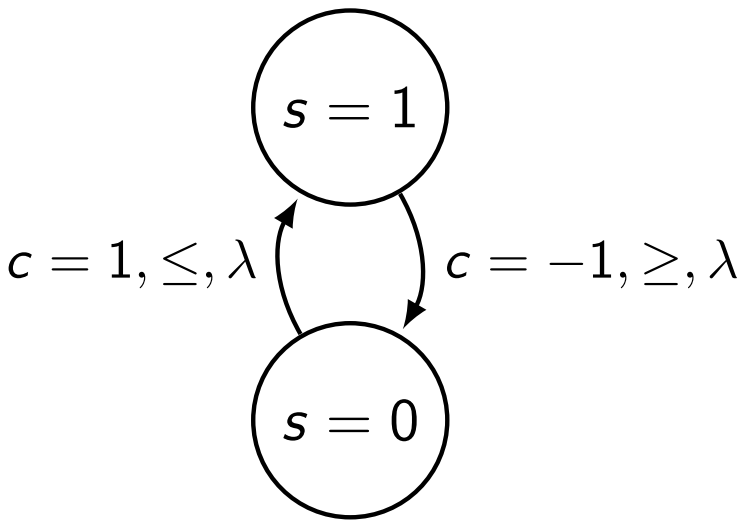
$$\underset{\substack{\mathbf{m}\in\mathbb{R}^N,\ \mathbf{s}\in\{0,1\}^N \\ \mathbf{c}\in\{-1,0,1\}^{N-1}}}{\text{minimize}} \quad \sum_{i=1}^{N} \ell(m_i, z_i) + \lambda \sum_{i=1}^{N-1} I(c_i \neq 0)$$

subject to

no change: $c_t = 0 \Rightarrow m_t = m_{t+1}$ and $s_t = s_{t+1}$

go up: $c_t = 1 \Rightarrow m_t \leq m_{t+1}$ and $(s_t, s_{t+1}) = (0, 1)$,

go down: $c_t = -1 \Rightarrow m_t \geq m_{t+1}$ and $(s_t, s_{t+1}) = (1, 0)$.



Nodes=states s,
Edges=changes c (constraint, penalty).

Generalized Functional Pruning Optimal Partitioning (GFPOP) algorithm for up-down constrained model

Recursively compute two vectors of real-valued cost functions:

$$\begin{array}{lll} \overline{C}_1(m_1) & \cdots & \overline{C}_N(m_N) \quad \text{optimal cost in peak state } s=1 \\ \underline{C}_1(m_1) & \cdots & \underline{C}_N(m_N) \quad \text{optimal cost in background state } s=0 \end{array}$$

$$\overline{C}_{t+1}(\mu) = \ell(\mu, z_i) + \min\{\overline{C}_t(\mu),\ \underline{C}_t^{\leq}(\mu) + \lambda\},$$

$$\underline{C}_{t+1}(\mu) = \ell(\mu, z_i) + \min\{\underline{C}_t(\mu),\ \overline{C}_t^{\geq}(\mu) + \lambda\},$$

where $f^{\leq}(\mu) = \min_{x \leq \mu} f(x)$,
$f^{\geq}(\mu) = \min_{x \geq \mu} f(x)$.