A Generalized Functional Pruning Optimal Partitioning (GFPOP) Algorithm for Peak Detection in Large Genomic Data

Toby Dylan Hocking
toby.hocking@nau.edu
joint work with
Guillem Rigaill, Guillaume Bourque, Paul Fearnhead

April 28, 2022

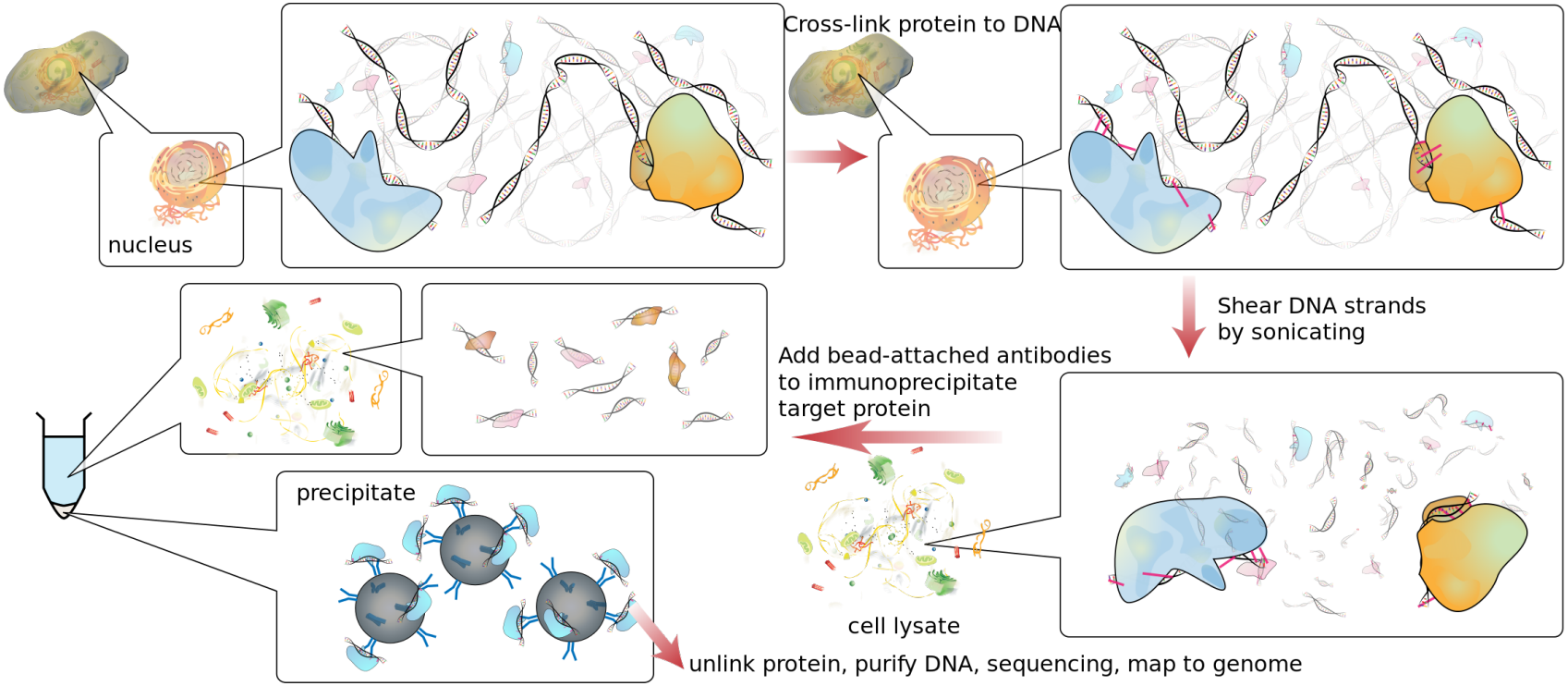
Problem: optimizing ChIP-seq peak detection

New functional pruning algorithm

Results on ChIP-seq benchmark

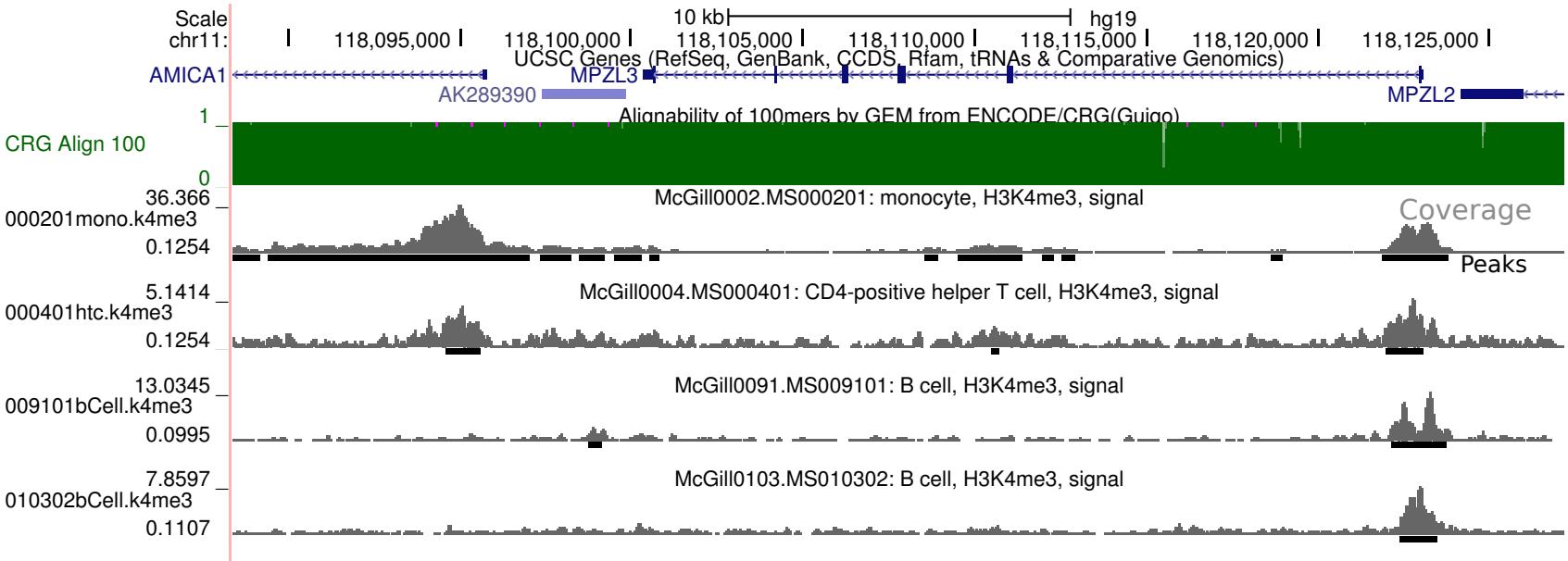
Chromatin immunoprecipitation sequencing (ChIP-seq)

Analysis of DNA-protein interactions.



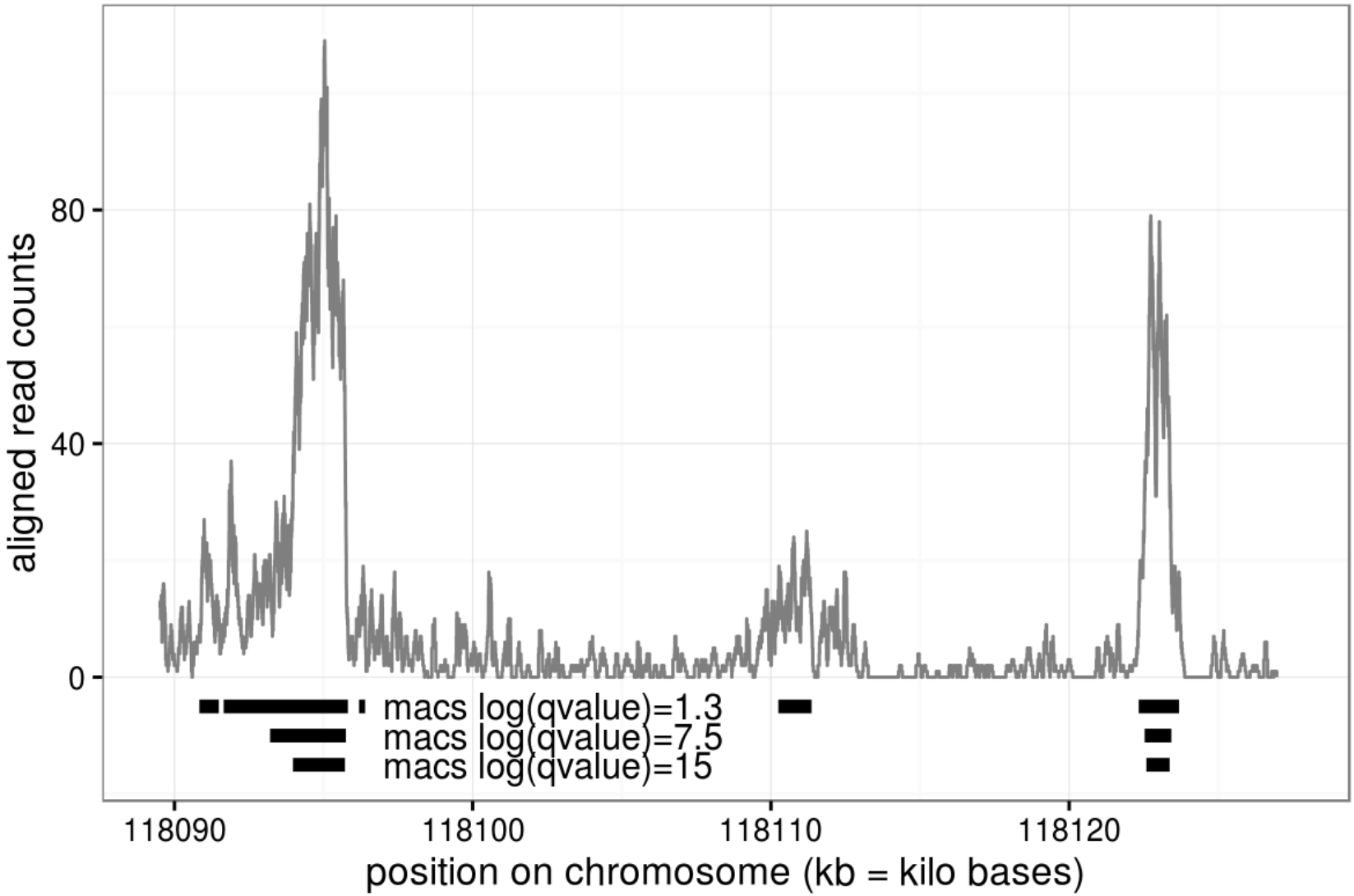
Source: "ChIP-sequencing," Wikipedia.

Problem: find peaks in each of several samples

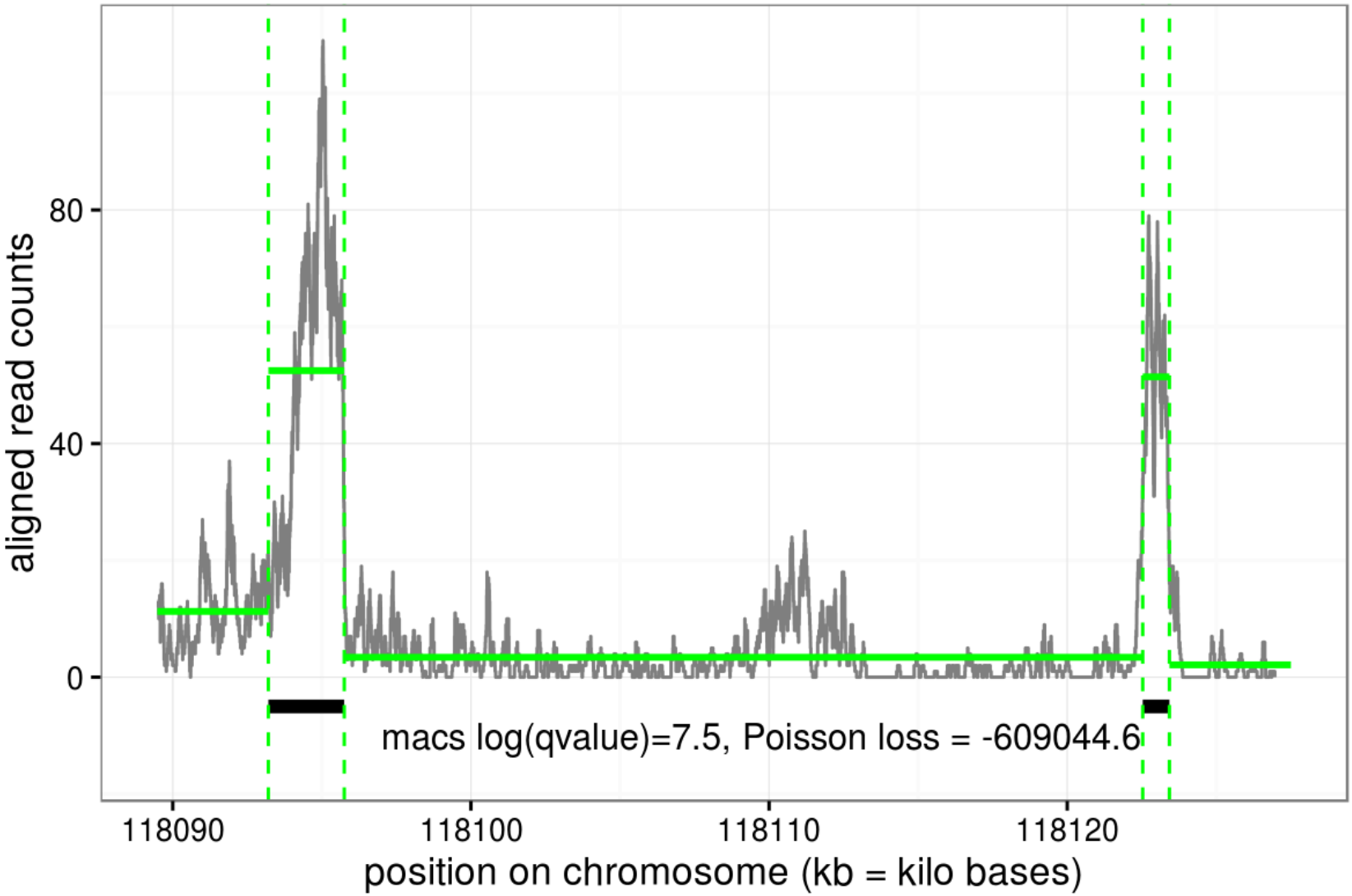


- Grey profiles are noisy aligned read count signals – peaks are genomic locations with protein binding sites.
- Black bars are peaks called by MACS2 (Zhang et al, 2008) – many false positives! (black bars where there is only noise)
- From a machine learning perspective, this is binary classification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

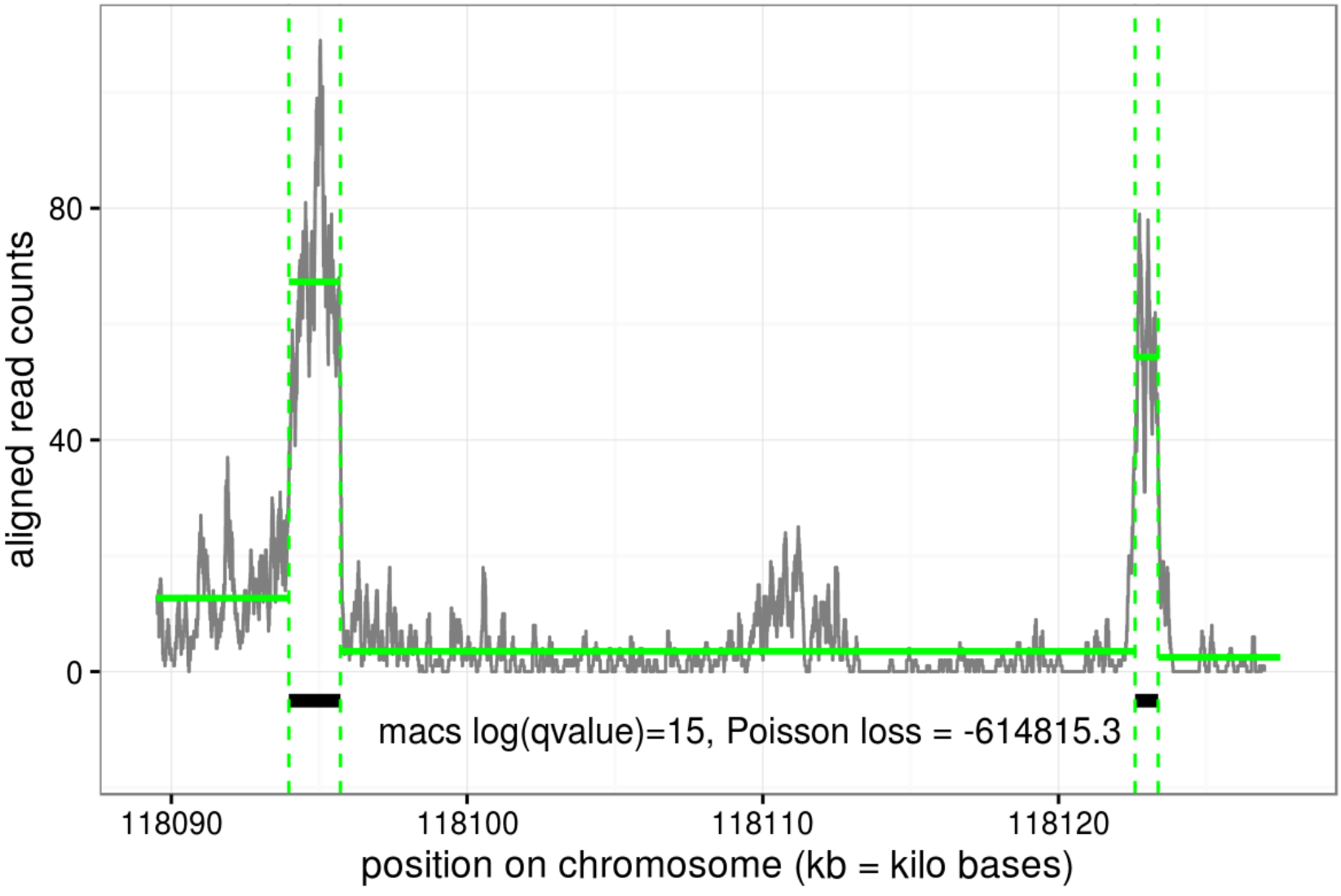
Which macs parameter is best for these data?



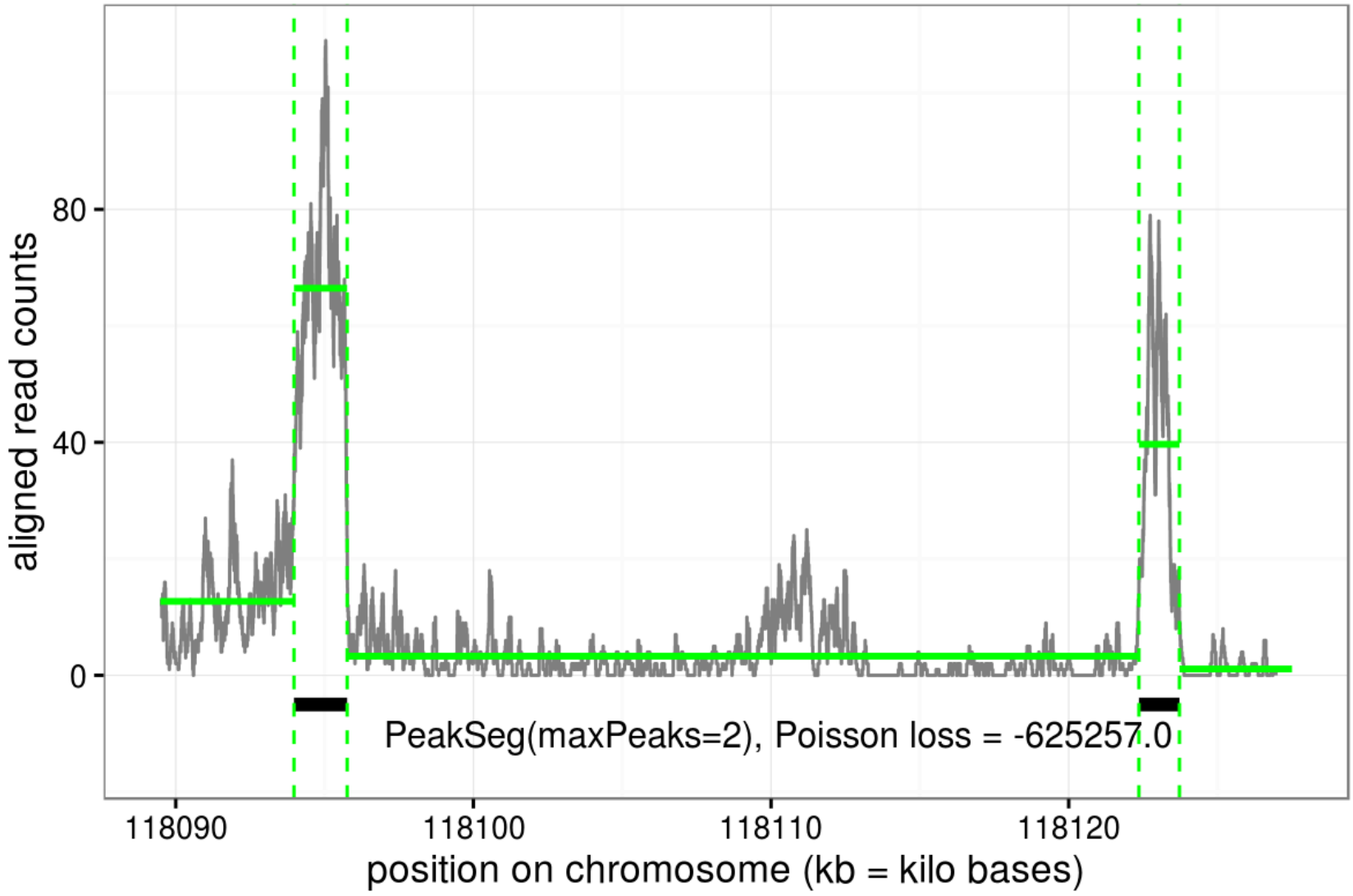
Compute likelihood/loss of piecewise constant model



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

Hocking *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: $\ell(u_s, z_i) = u_s - z_i \log u_s$.

Maximum likelihood changepoint detection with up-down constraints on adjacent segment means (PeakSeg)

$$\begin{aligned} &\underset{\substack{\mathbf{u}\in\mathbb{R}^S \\ 0=t_0<t_1<\cdots<t_{S-1}<t_S=N}}{\text{minimize}} && \sum_{s=1}^{S}\sum_{i=t_{s-1}+1}^{t_s} \ell(u_s, z_i) \\ &\text{subject to} && u_{s-1} \leq u_s \ \forall s \in \{2,4,\dots\}, \\ & && u_{s-1} \geq u_s \ \forall s \in \{3,5,\dots\}. \end{aligned}$$

- Simple: 1 parameter = number of segments $S \in \{1,3,\dots\}$.
- Hard optimization problem, naively $O(N^S)$ time.
- Previous unconstrained model: not always up-down changes.
- Interpretable: $P = (S-1)/2$ peaks (segments 2, 4, ...).
- H *et al.*, *ICML* 2015: $O(SN^2)$ time approximate algorithm.
- H *et al.*, arXiv 2017: $O(SN \log N)$ time optimal algorithm.

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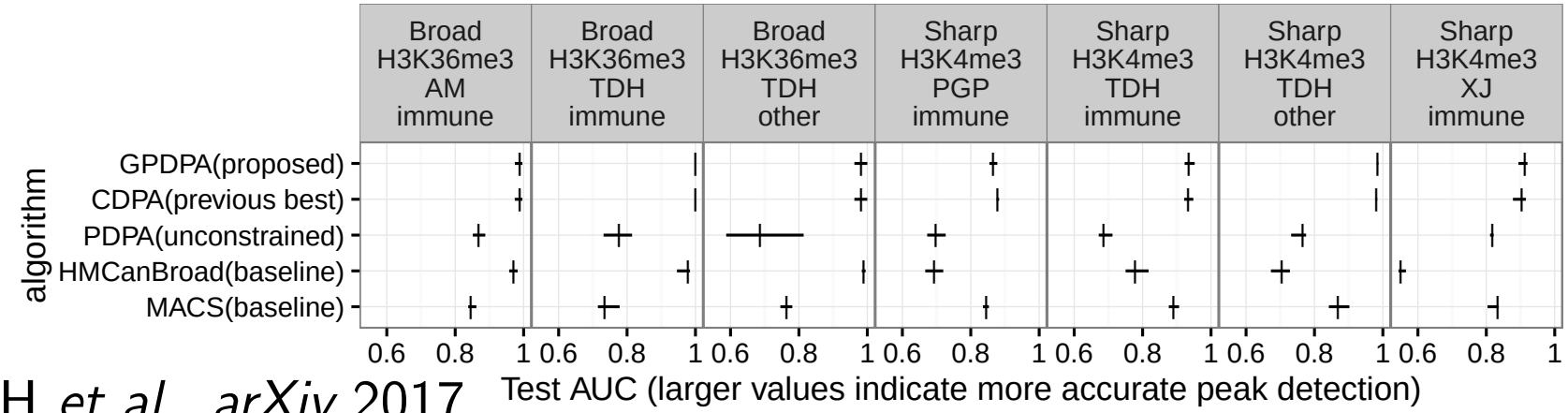
Dynamic programming with up-down constraints is highly accurate for both broad and sharp data/pattern types



H *et al.*, *arXiv* 2017.

- 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).

Problem: optimizing ChIP-seq peak detection

New functional pruning algorithm

Results on ChIP-seq benchmark

Previous work on the Segment Neighborhood problem

	no pruning	functional pruning
unconstrained	Dynamic Prog. Algo. exact $O(SN^2)$ Auger and L. 1989	Pruned DPA exact $O(SN \log N)$ Rigaill 2010
up-down constrained	Constrained DPA inexact $O(SN^2)$ H et al 2015	Generalized PDPA exact $O(SN \log N)$ H et al 2017

- 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:

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

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

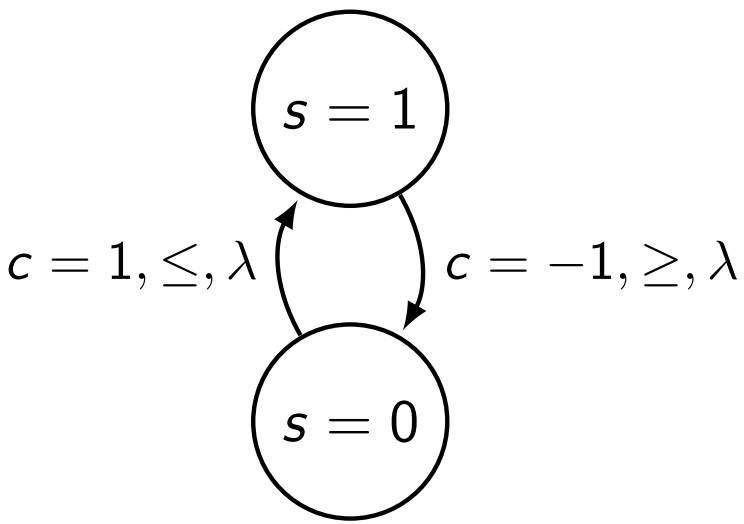
$$\underset{\substack{\mathbf{m}\in\mathbb{R}^N,\ \mathbf{s}\in\{0,1\}^N \\ \mathbf{c}\in\{-1,0,1\}^{N-1}}}{\text{minimize}} \quad \sum_{i=1}^{N} \ell(m_i, z_i) + \lambda \sum_{i=1}^{N-1} I(c_i \neq 0)$$

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

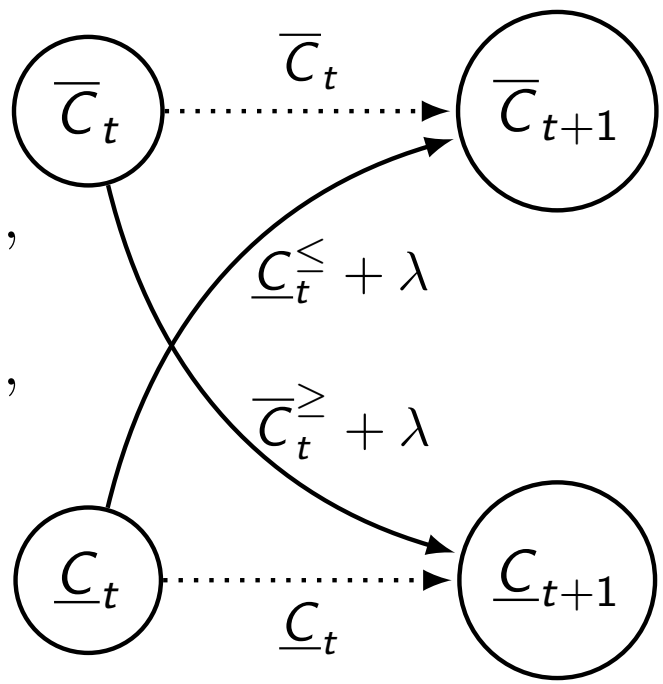
Recursively compute two vectors of real-valued cost functions:

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

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

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

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



Problem: optimizing ChIP-seq peak detection

New functional pruning algorithm

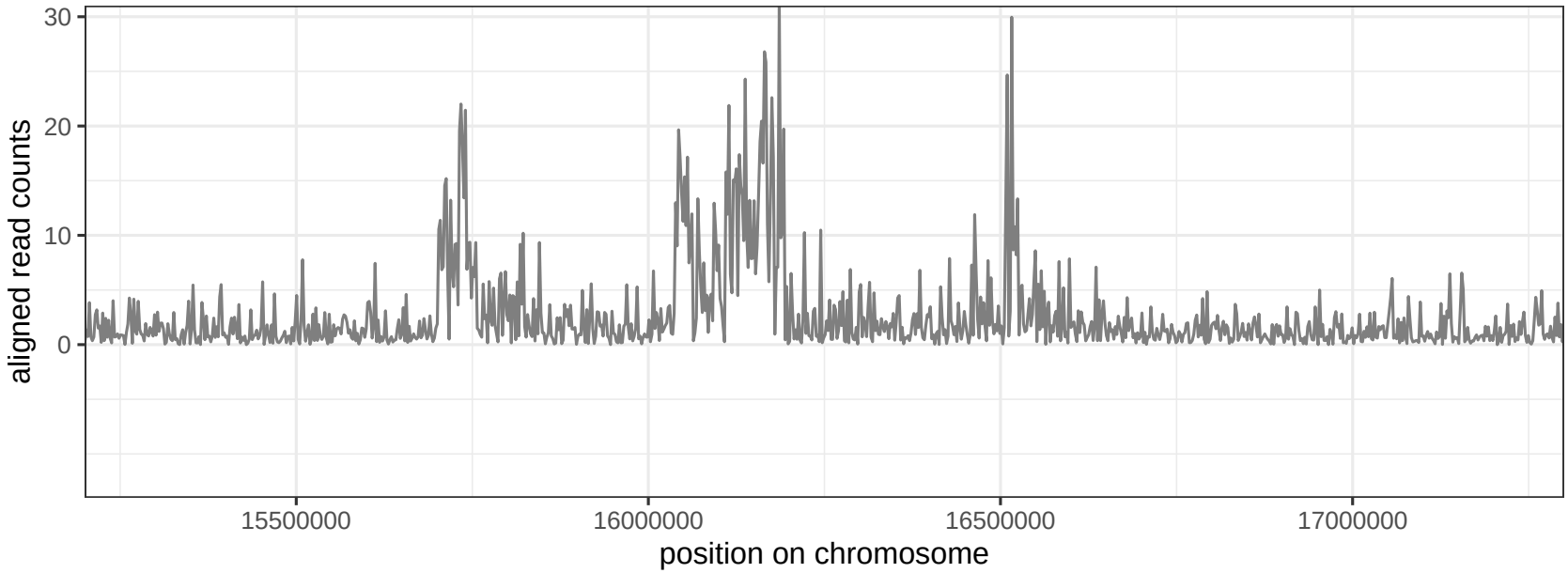
Results on ChIP-seq benchmark

Benchmark of large genomic data sequences

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

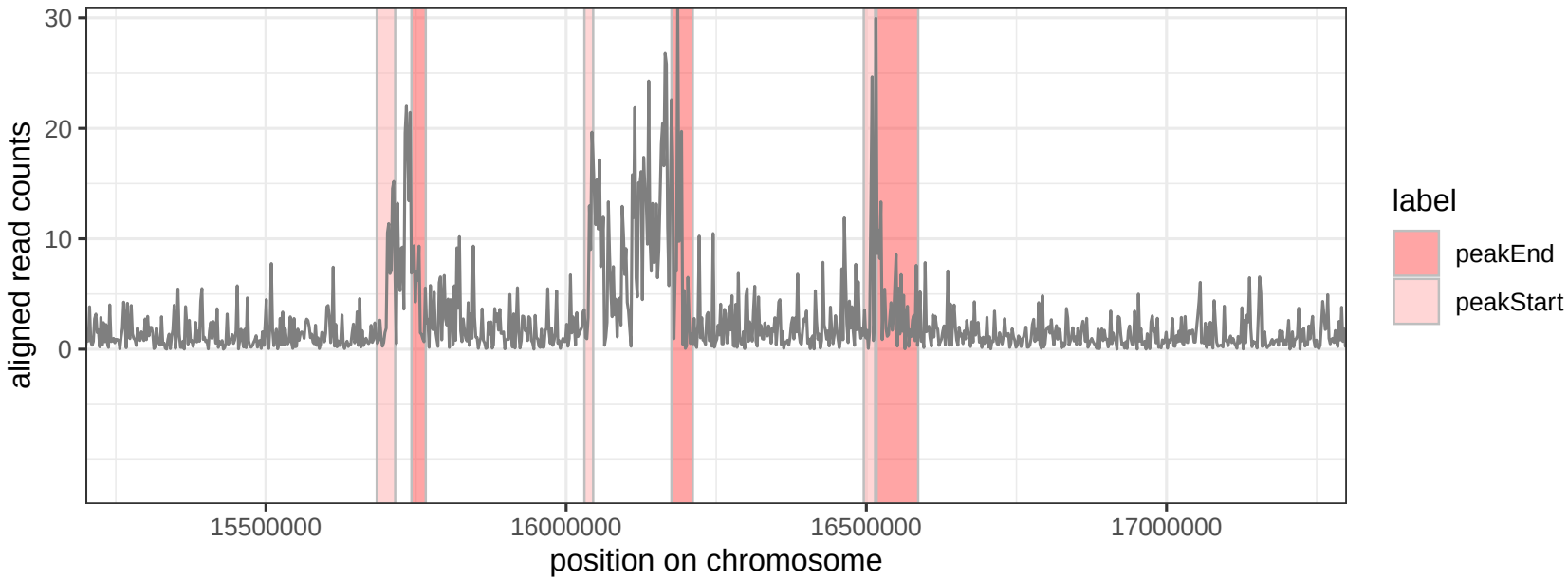
- 4951 data sequences ranging from $N = 10^3$ to $N = 10^7$.
- Ran GFPOP with penalty $\lambda \in (\log N, N)$, resulting in a range of models with different numbers of peaks, for each data set.
- Each data set has **labels** which can be used to determine an appropriate number of peaks.

Labels used to determine optimal number of peaks



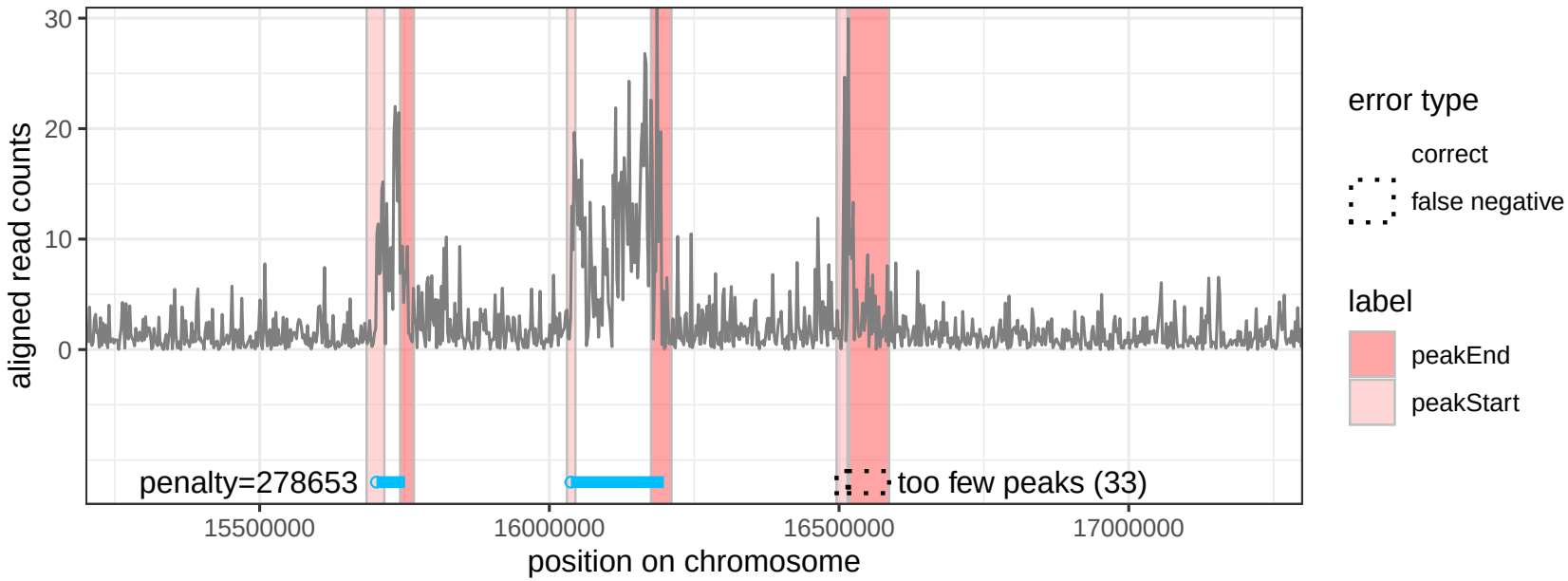
One ChIP-seq data set with $N = 1,254,751$ (only 82,233 shown).

Labels used to determine optimal number of peaks



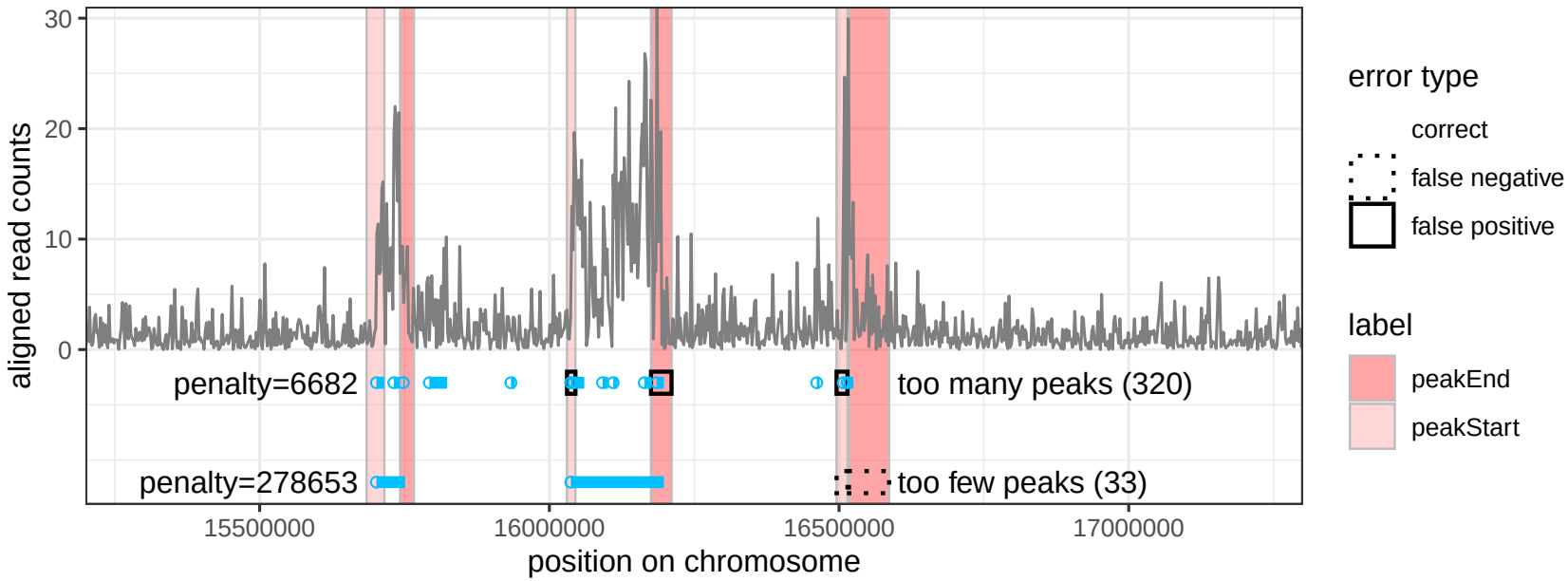
Visually labeled regions (H *et al.*, *Bioinformatics* 2017).

Labels used to determine optimal number of peaks



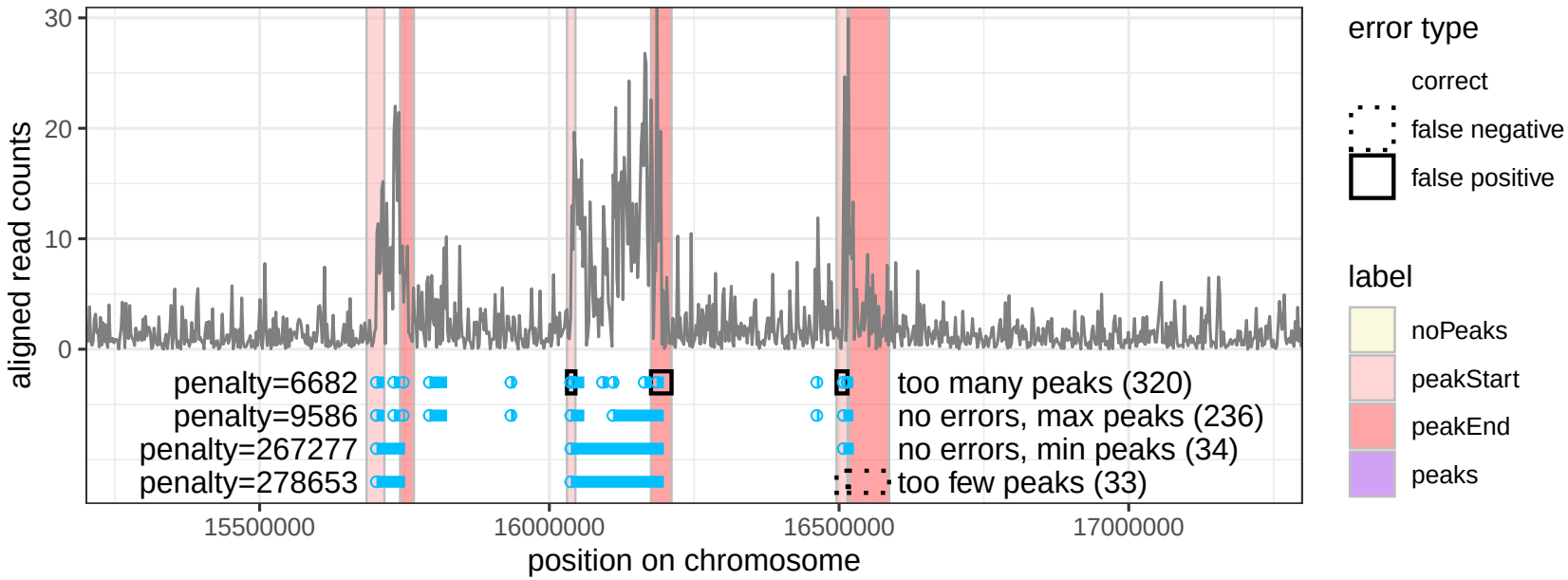
Penalty too large, too few peaks, 2 false negative labels.

Labels used to determine optimal number of peaks



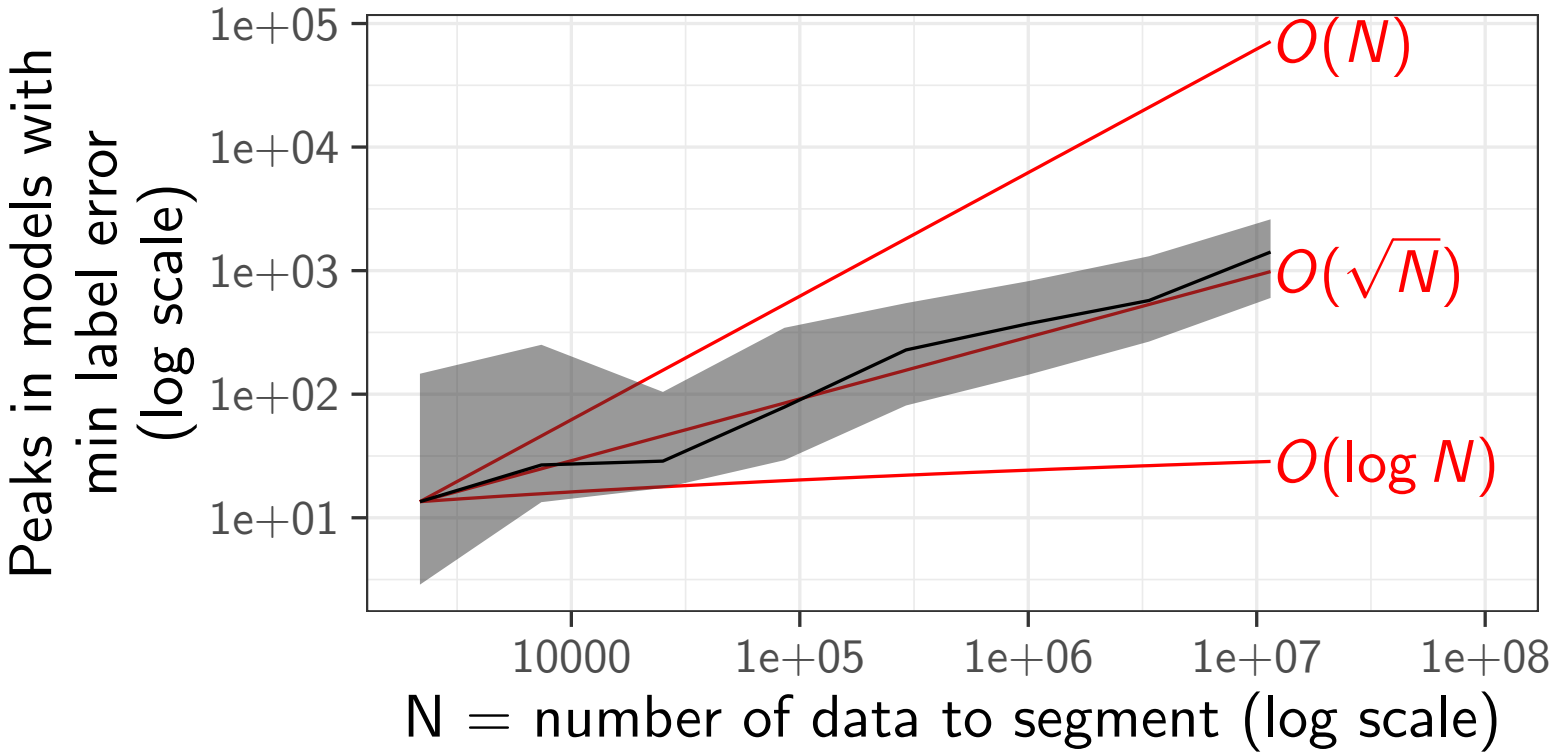
Penalty too small, too many peaks, 3 false positive labels.

Labels used to determine optimal number of peaks



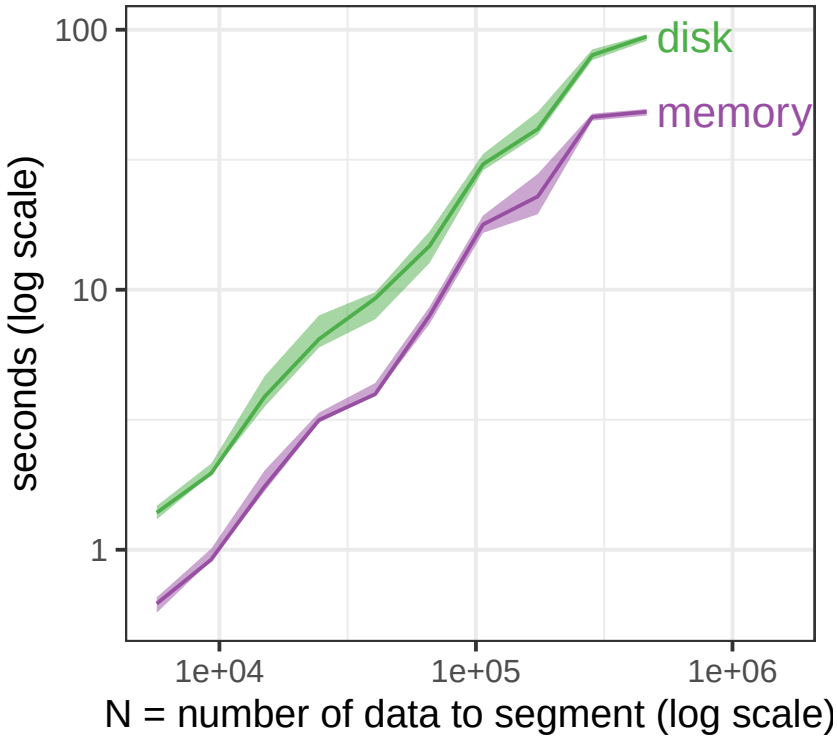
Models with 34–236 peaks have no label errors (midpoint=135).

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 means 220 TB of storage space and 17 weeks of computation time!

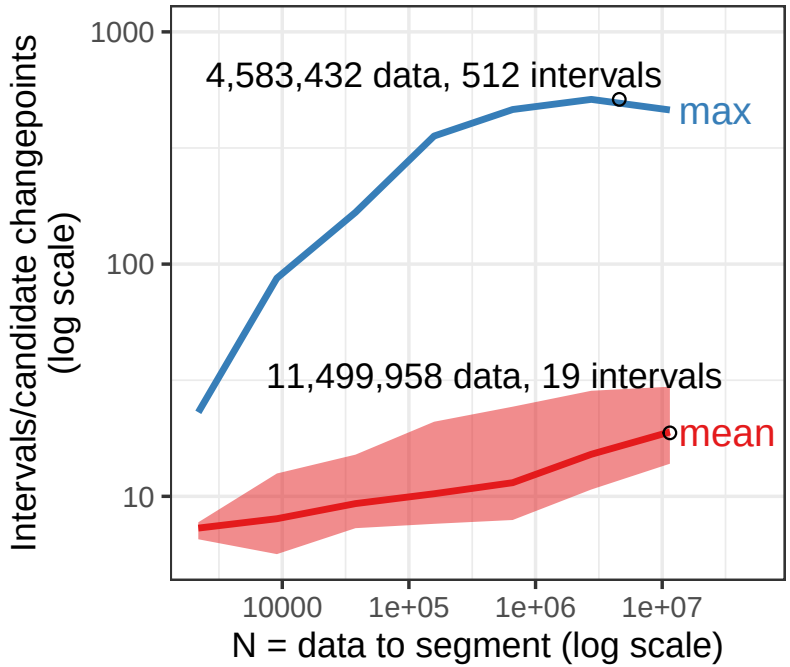
GFPOP Implementation stores cost functions on disk

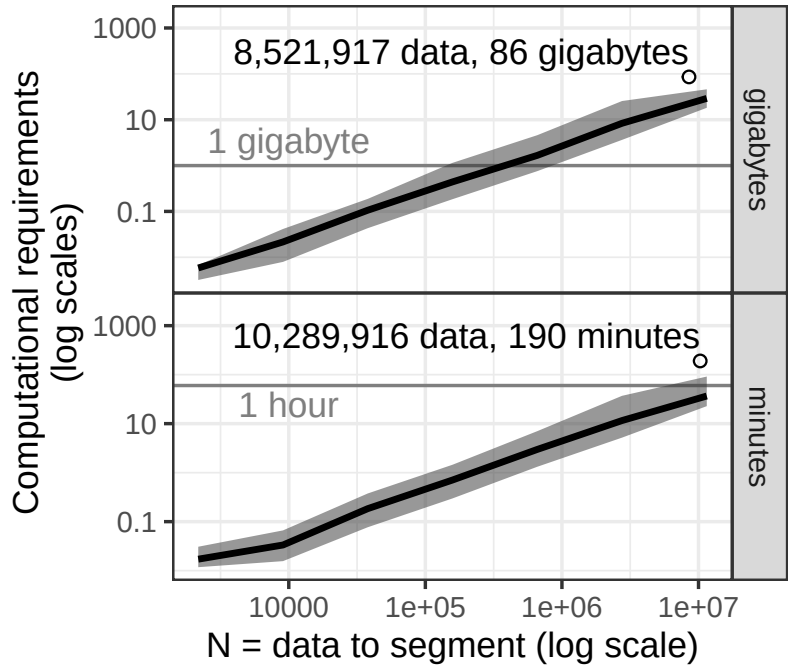


- Disk storage is only a constant factor slower than memory!
- Both are $O(N \log N)$ time.
- Memory implementation: $O(N \log N)$ memory! (too big)
- Disk implementation: $O(\log N)$ memory (< 1GB), $O(N \log N)$ disk.

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 $\overline{C}_t(\mu)$.





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

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

But how to compute model with $O(\sqrt{N})$ peaks?

Binary 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.

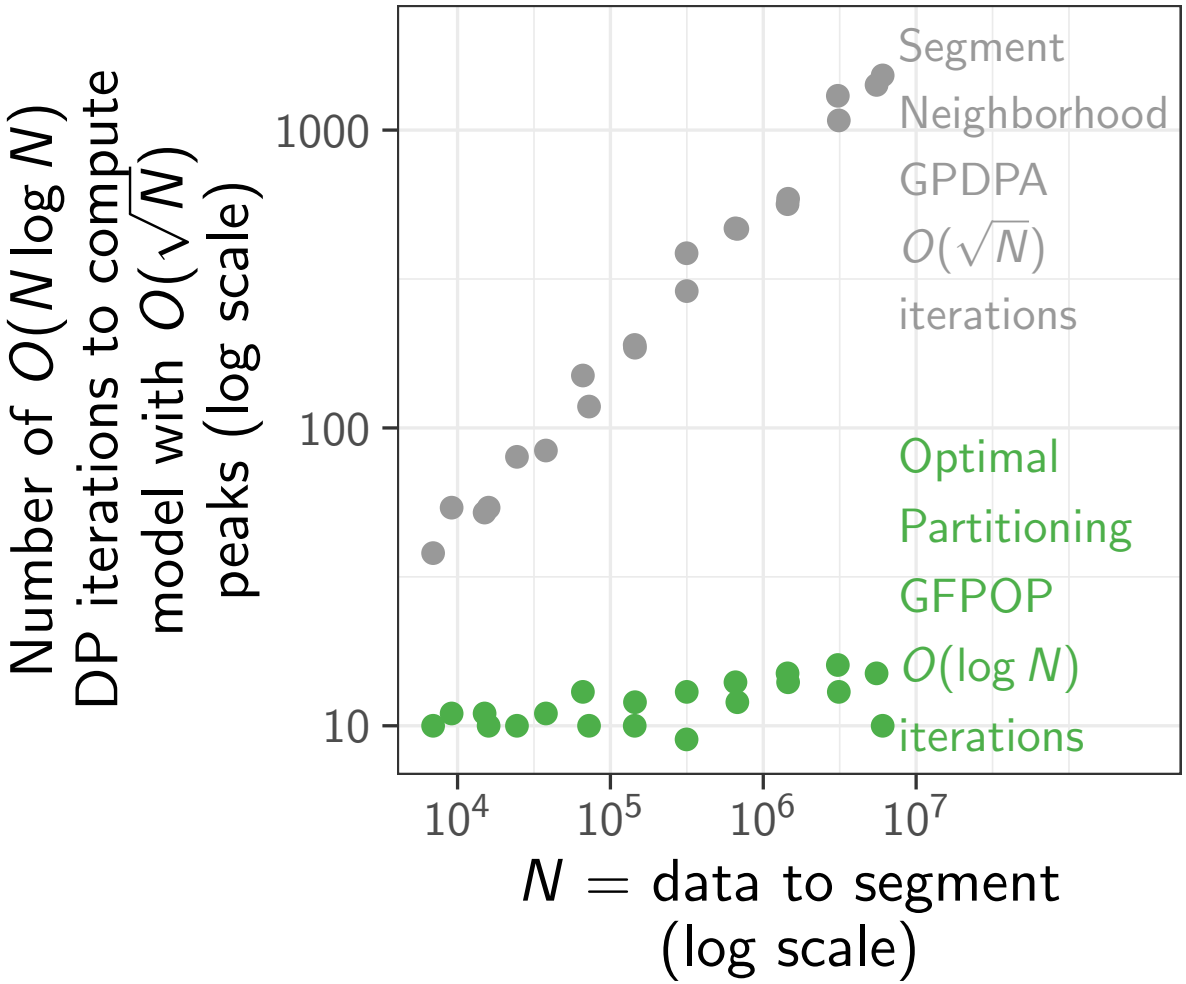
Example run of binary search algorithm using GFPOP

One data set with $P^* = 93$ peaks and $N = 146,186$ data.

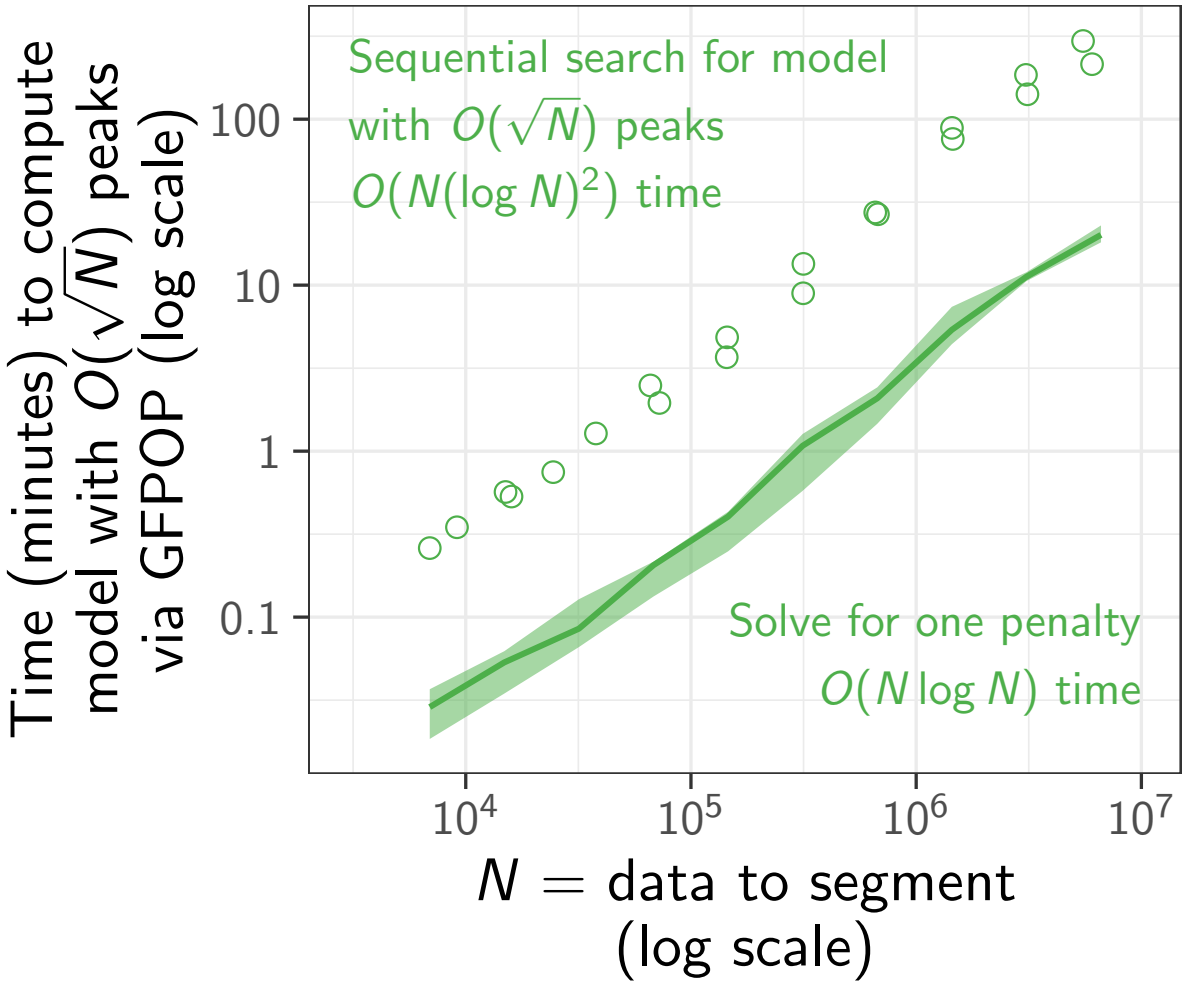
iteration	$\underline{p}$	$\overline{p}$	λ	p_{new}	L_{new}
1			0	68752	-2570319
1			∞	0	14239212
2	0	68752	244.4952	4361	1980119
3	0	4361	2811.0738	188	3676671
4	0	188	56183.7271	55	5330310
5	55	188	12433.3766	98	4108354
6	55	98	28417.5941	72	4584042
7	72	98	18295.6895	83	4336773
8	83	98	15227.9249	90	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

12 DP iterations much fewer than $93 \times 2 = 186$ which would be required for Segment Neighborhood!

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



Binary 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)

Conclusions

- Previous GPDPA was $O(N\sqrt{N}\log N)$ – much too complex to compute a zero-error model with $O(\sqrt{N})$ peaks for $N = 10^7$ data.
- Proposed GFPOP with binary search is $O(N(\log N)^2)$ time, $O(\log N)$ memory, $O(N \log N)$ disk – optimal models are now possible to compute for large data.
- C++ code with R interface:
  `PeakSegPipeline::PeakSegFPOP_disk`
  `https://github.com/tdhock/PeakSegPipeline`
- Future work: changepoint detection in large ecological data?
- 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.