A qsub pipeline for supervised ChIP-seq peak detection

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joint work with Guillem Rigaill and Guillaume Bourque

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ChIP-seq data and previous work on unsupervised peak detection

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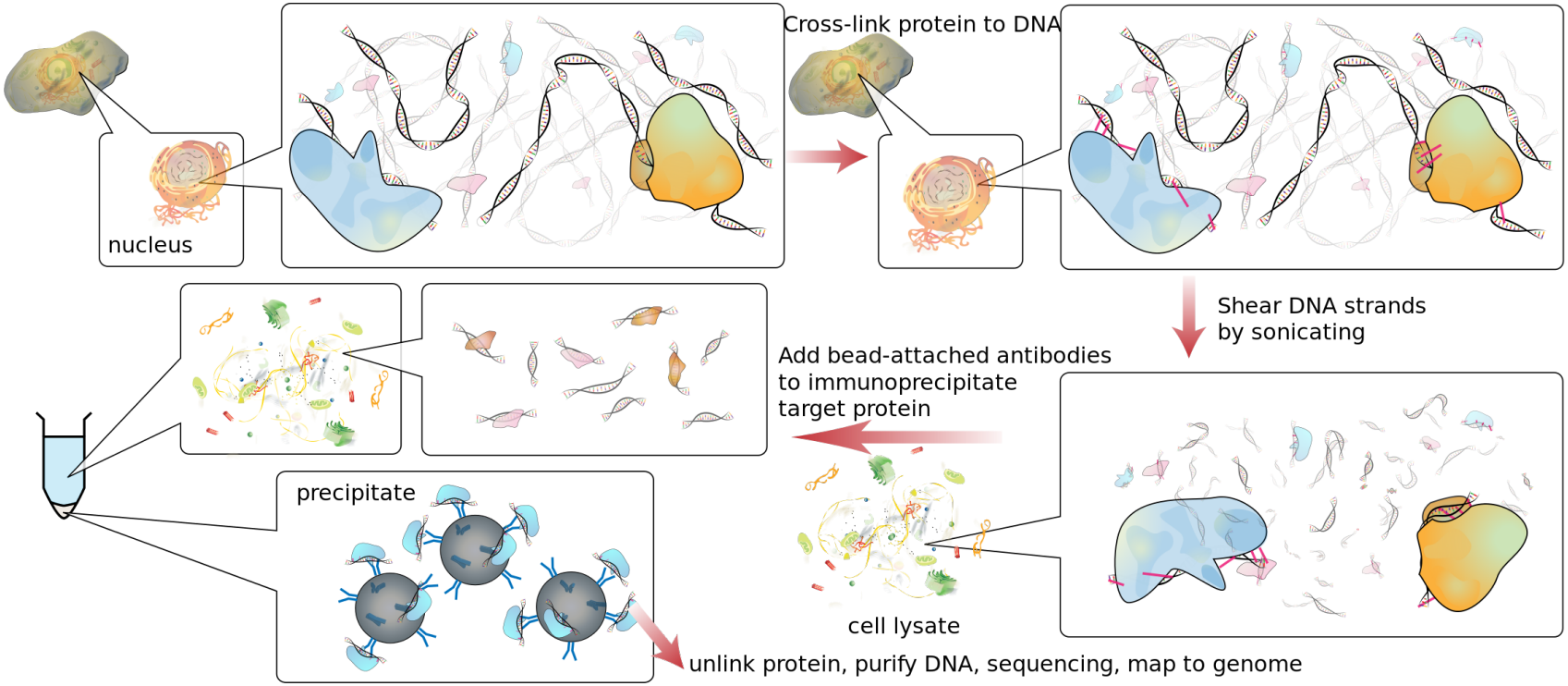
Results on the McGill benchmark data set, conclusions

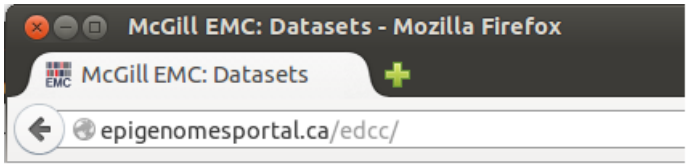
Chromatin immunoprecipitation sequencing (ChIP-seq)

Analysis of DNA-protein interactions.



Source: "ChIP-sequencing," Wikipedia.

Data downloaded from Epigenomes Portal



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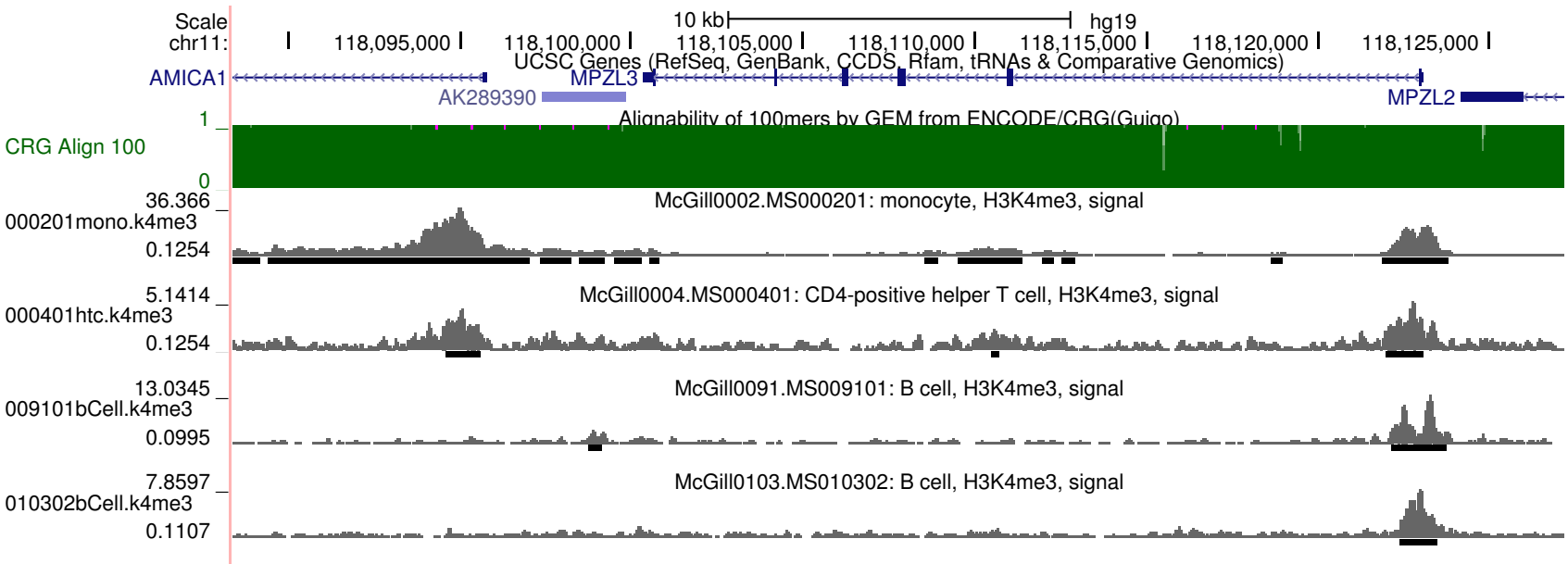
EPIGENOMICS MAPPING CENTRE

	Histone						Methylome	Transcriptome		
	H3K27ac	H3K27me3	H3K36me3	H3K4me1	H3K4me3	H3K9me3	Input	WGB-Seq	RNA-Seq	mRNA-Seq	smRNA-Seq
B cell - Blood	1	1	1	2	2		2	1	35		
Brain - Brain									3		
Eosinophils - Blood								3			
Kidney - Kidney	1	1	1	1	1		1	1	1		
Kidney (Renal Carcinoma) - Kidney	1	1	1	1	1	1	1				
Leukemia CD19+CD10+ B Cells - Blood	1			1	1	1	2	2	2		
Monocytes - Blood	6	4	8	8	6	7	11	4	75		2
Naive CD4+ T Cells - Blood									29	39	
Renal Cancer - Kidney								1	1		
Skeletal Muscle (Control) - Muscle	3	2	3	1	3	3	3	7	14		
Skeletal Muscle (Mitochodrial Disease) - Muscle	5	5	5	4	4	3	5	8	14		
T cells - Blood	15	16	16	18	19	14	22	16	66		4

Visualize in Genome Browser | Get track hub link | Download tracks

Goal: find peaks in each of several samples



Existing unsupervised peak detection algorithms

- Model-based analysis of ChIP-Seq (MACS), Zhang et al, 2008.
- SICER, Zang et al, 2009.
- HOMER findPeaks, Heinz et al, 2010.
- RSEG, Song and Smith, 2011.
- Histone modifications in cancer (HMCan), Ashoor et al, 2013.
- ... dozens of others.

Two big questions: how to choose the best...

- ...algorithm?
- ...parameters?

Problem: how to choose model parameters?

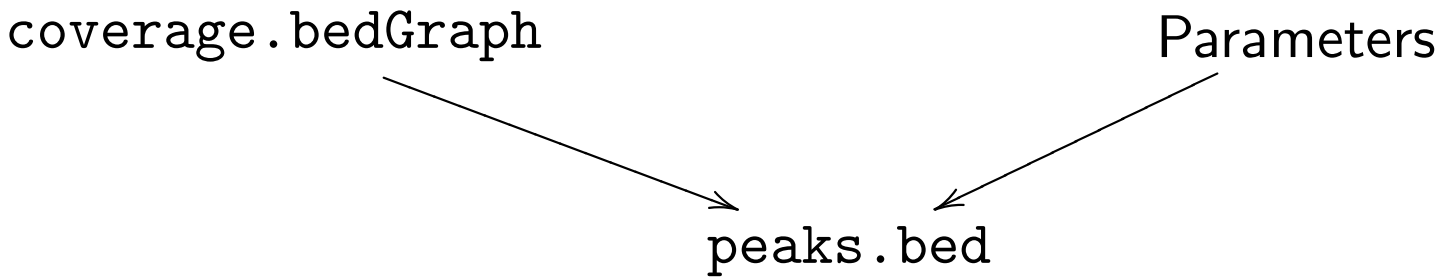
19 parameters for Model-based analysis of ChIP-Seq (MACS), Zhang et al, 2008.

```
[-g GSIZE]
[-s TSIZE] [--bw BW] [-m MFOLD MFOLD] [--fix-bimodal]
[--nomodel] [--extsize EXTSIZE | --shiftsize SHIFTSIZE]
[-q QVALUE | -p PVALUE | -F FOLDENRICHMENT] [--to-large]
[--down-sample] [--seed SEED] [--nolambda]
[--slocal SMALLLOCAL] [--llocal LARGELOCAL]
[--shift-control] [--half-ext] [--broad]
[--broad-cutoff BROADCUTOFF] [--call-summits]
```

10 parameters for Histone modifications in cancer (HMCan), Ashoor et al, 2013.

```
minLength 145
medLength 150
maxLength 155
smallBinLength 50
largeBinLength 100000
pvalueThreshold 0.01
mergeDistance 200
iterationThreshold 5
finalThreshold 0
maxIter 20
```

Summary of unsupervised peak detectors



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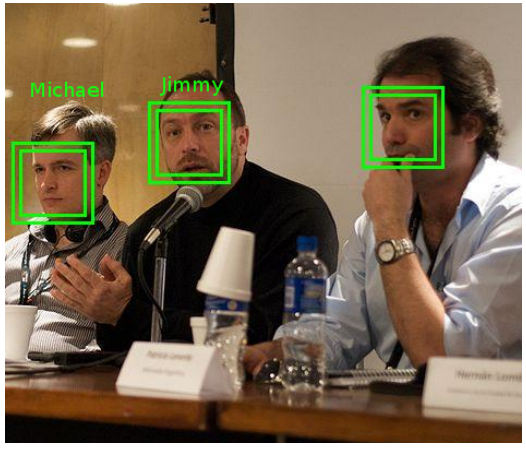
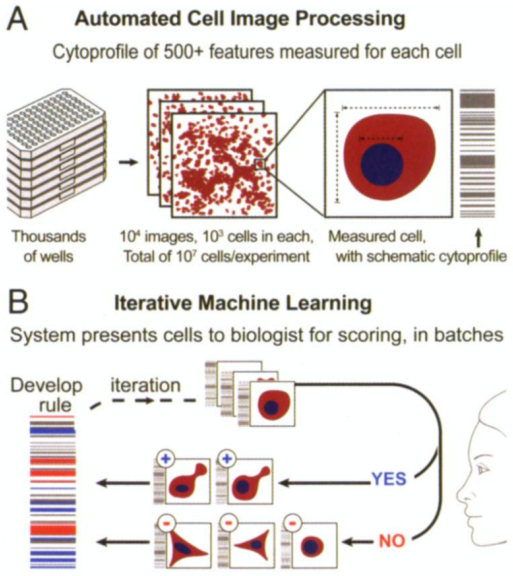
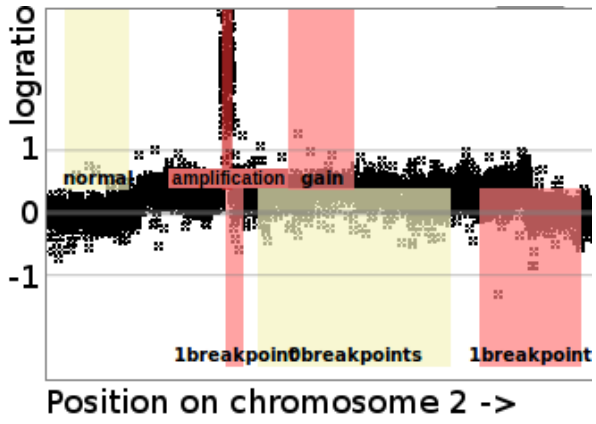
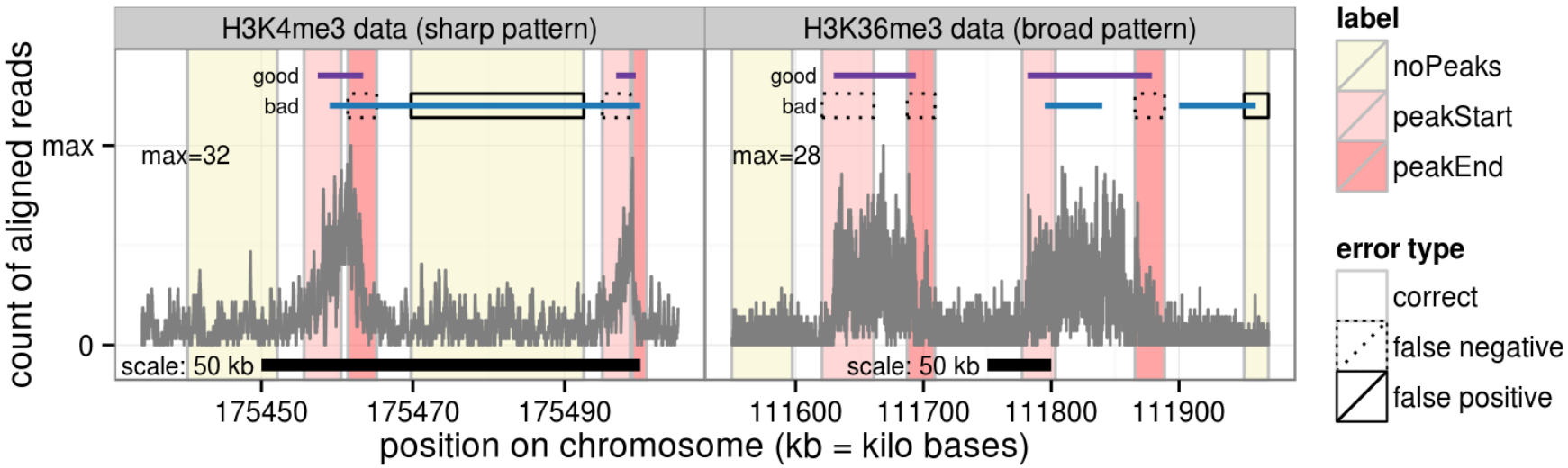
Previous work in computer vision: look and add labels to...

Photos	Cell images	Copy number profiles
		
Labels: names	phenotypes	alterations
CVPR 2013 246 papers	CellProfiler 873 citations	SegAnnDB H, *et. al.* 2014.

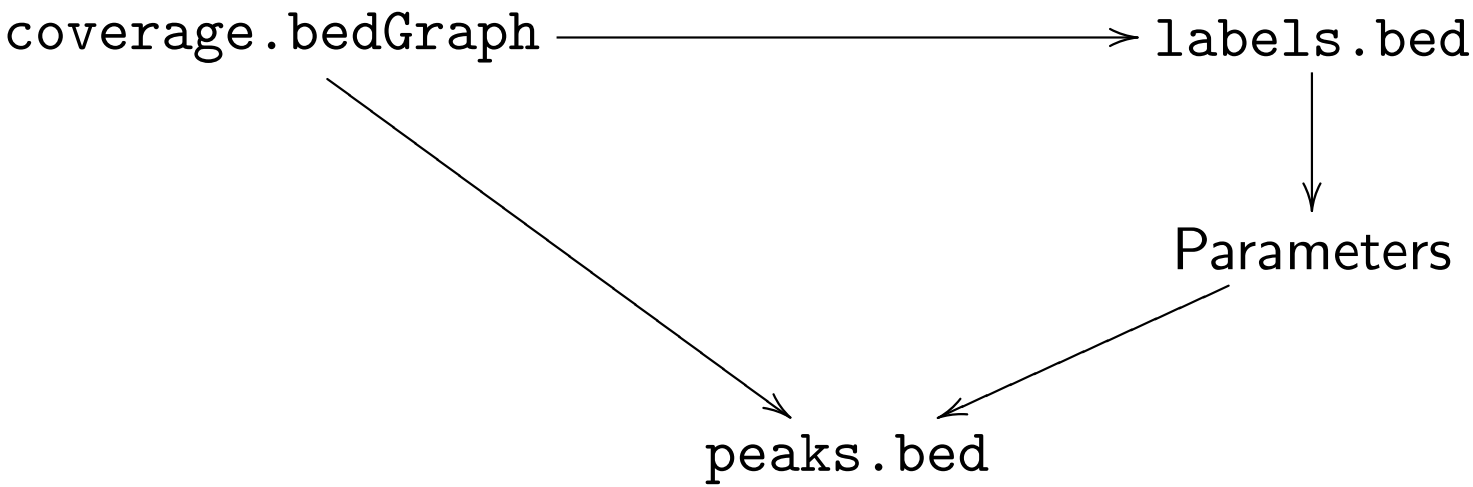
Sources: `http://en.wikipedia.org/wiki/Face_detection`
Jones et al PNAS 2009. Scoring diverse cellular morphologies in image-based screens with iterative feedback and machine learning.

Peak detector accuracy can be quantified using manually annotated region labels

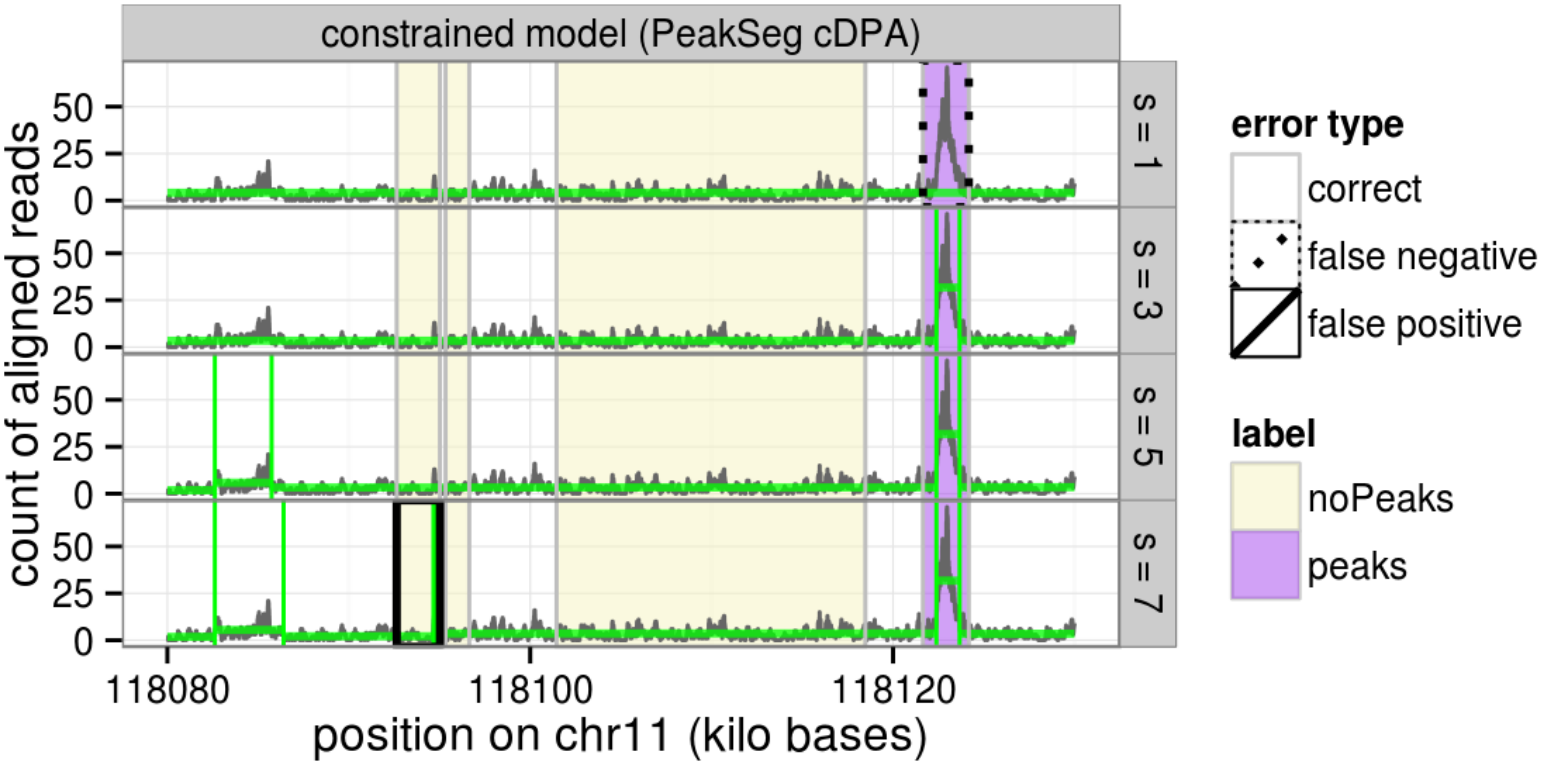


- Good peaks have 0 incorrect regions.
- Bad peaks have 7 incorrect regions.
- Goal: minimize number of incorrect regions.

Summary of supervised peak detection



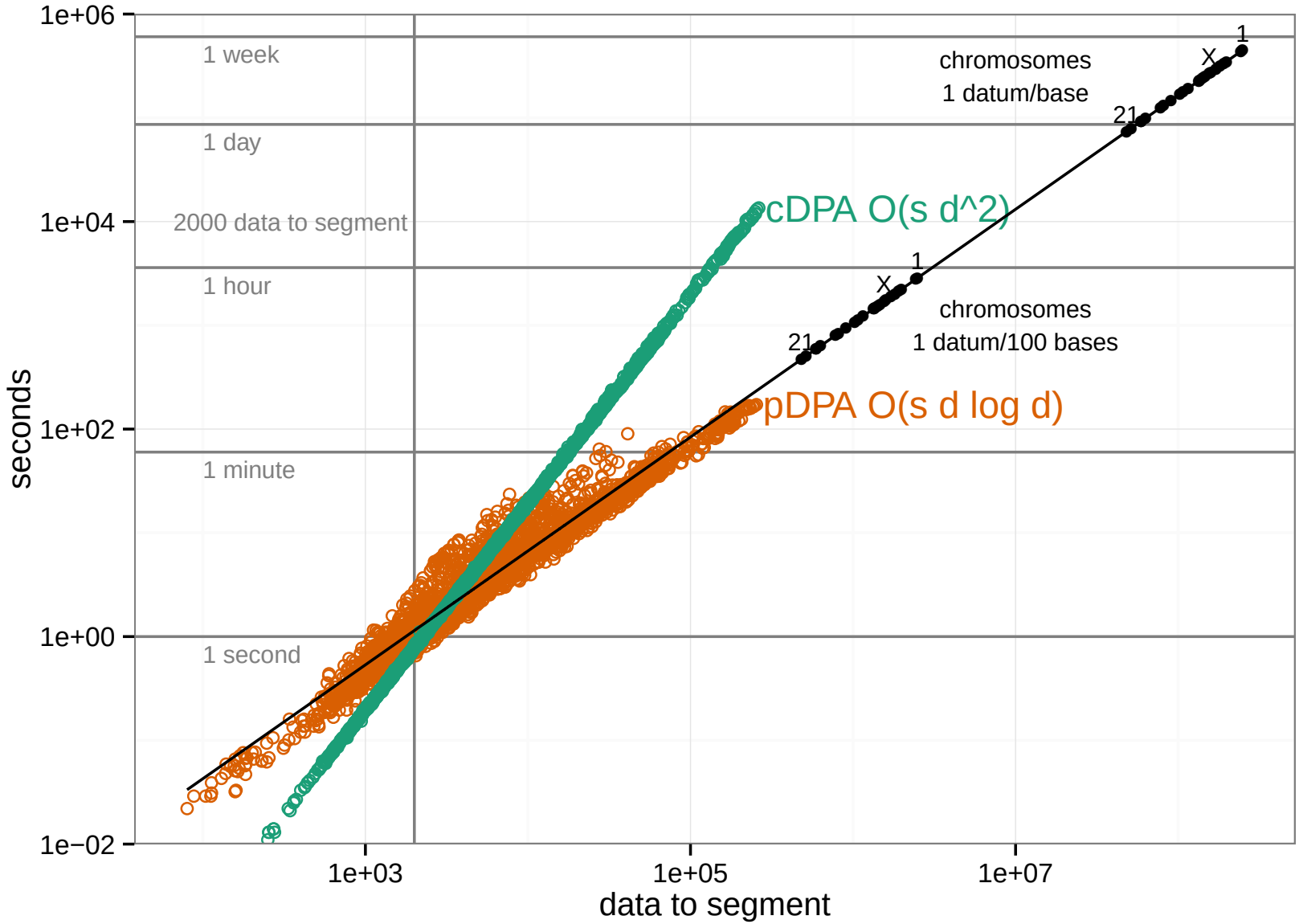
PeakSeg constrained maximum likelihood model



State-of-the-art peak detection (Hocking et al, ICML2015), but constrained Dynamic Programming Algorithm = cDPA has $O(s_{\max} d^2)$ time complexity:

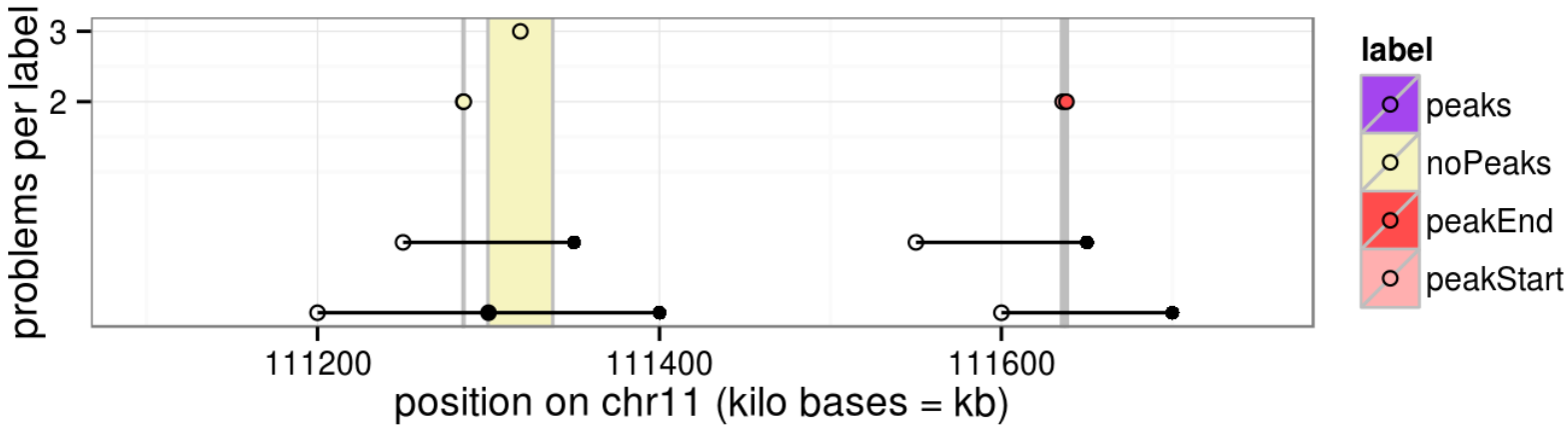
- $s_{\max}$ = maximum number of segments/peaks,
- d = data points to segment.

Timings on benchmark data sets



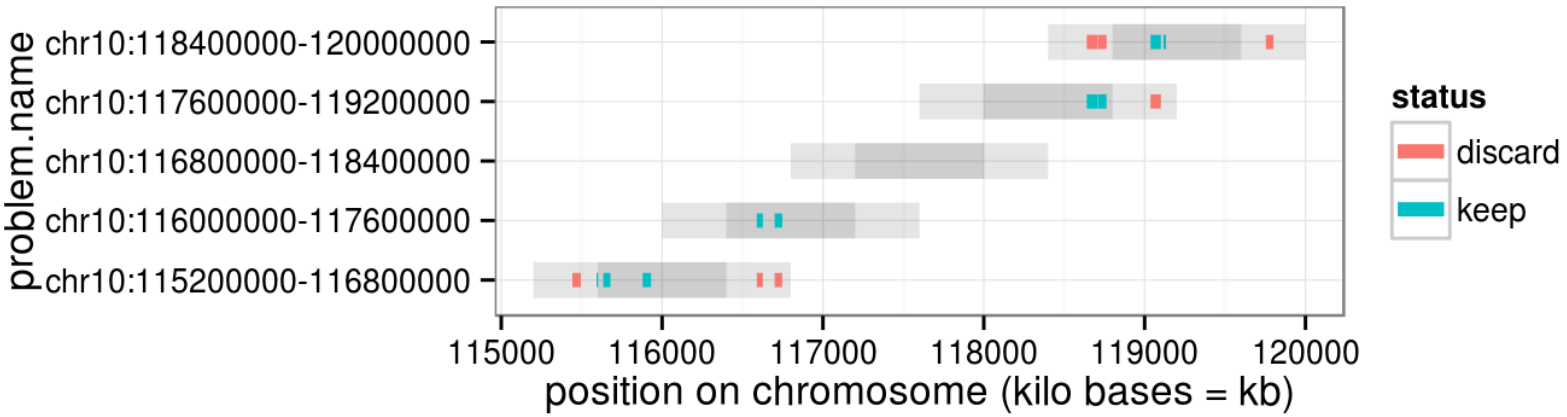
How to use cDPA on whole genome?

Break the genome into separate segmentation problems



Segmentation problems (black) with labeled regions (colors).

Only keep peaks in the center of each problem



Segmentation problems (light grey)
with regions where peaks are kept (dark grey).

Summary of proposed PeakSeg model

- Fix $d = 2000$ data points (bins) per segmentation problem.
- Split the genome into separate segmentation problems of size R.
- Try several different resolutions R,
  select the resolution R with minimal train error.
- Learn the PeakSeg model using the labeled problems.
- Use the model to predict peaks on all problems.

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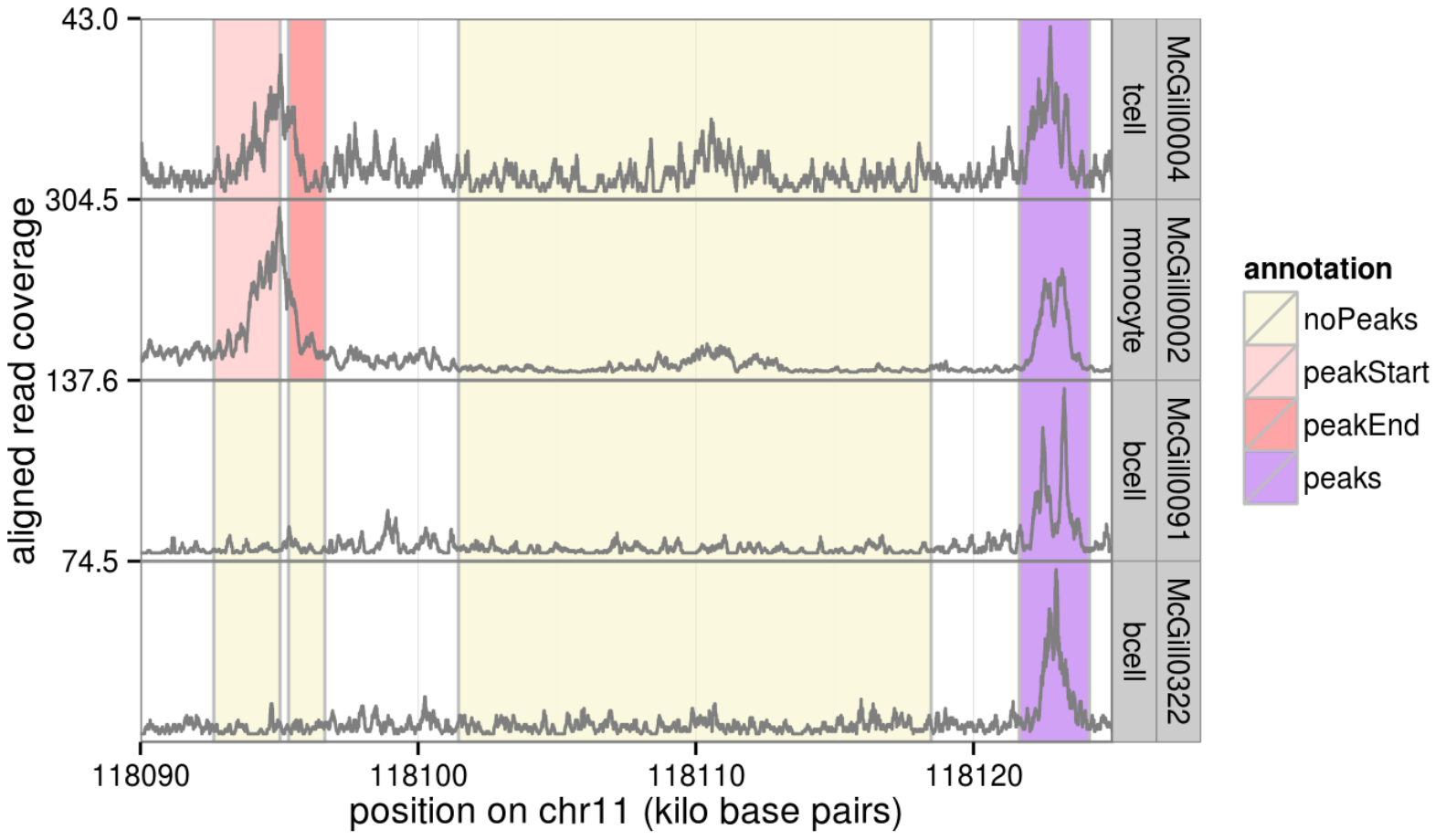
Label regions with and without peaks in several samples



Input labels file determined by visual inspection

```
chr11:118,092,641-118,095,026 peakStart tcell monocyte
chr11:118,095,334-118,096,640 peakEnd tcell monocyte
chr11:118,101,452-118,118,472 noPeaks
chr11:118,121,649-118,124,175 peaks tcell monocyte bcell

chr11:117,197,077-117,200,591 peaks tcell bcell
chr11:117,190,651-117,196,415 noPeaks
chr11:117,149,810-117,152,933 peaks tcell
```

- Used UCSC genome browser or IGV.
- Two newlines separate groups of nearby regions.
- Write only cell types with peaks.
- Labels: peaks, peakStart, peakEnd, noPeaks.

Input: project organized by cell type

```
exampleData/
exampleData/manually_annotated_region_labels.txt
exampleData/bcell/
exampleData/bcell/McGill0091.bedGraph
exampleData/bcell/McGill0322.bedGraph
exampleData/tcell/
exampleData/tcell/McGill0095.bedGraph
exampleData/tcell/McGill0107.bedGraph
```

qsub pipeline steps

For n samples, `00_AllSteps_qsub.R` launches

jobs	time per job	script
0	seconds	Step0-convert-labels.R
n	5–60 minutes*	Step1-segment-labeled-regions.R
1	5–30 minutes	Step2-learn-model-complexity.R
n	1–10 hours*	Step3-predict-peaks.R
1	5–15 minutes	Step4-cluster-peaks.R

* depends on optimal resolution.

Wait for jobs to finish:

```
#PBS -W depend=afterok:1001:1002:1003
```

TODO: demo and example output

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Benchmark labeled data sets

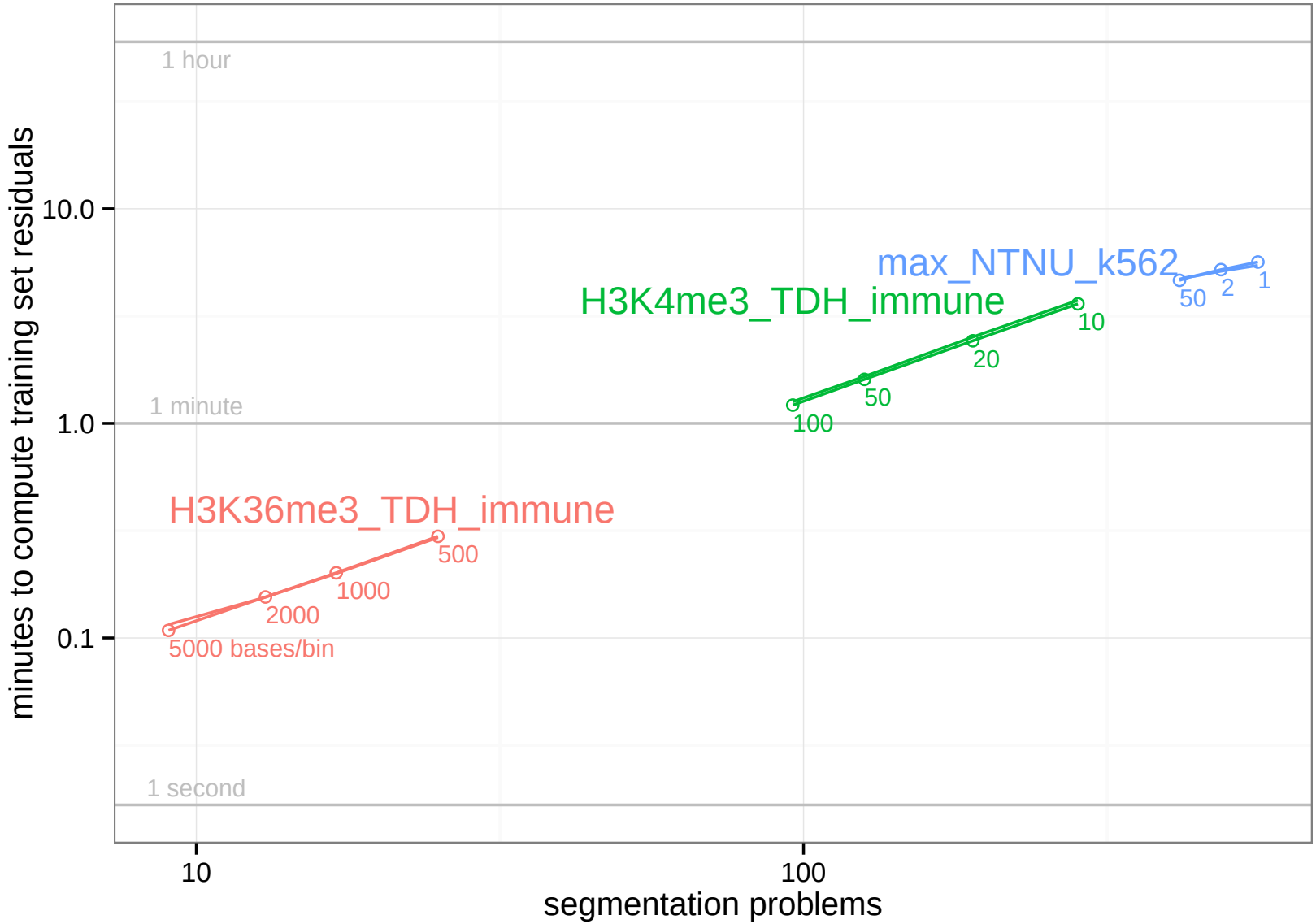
`http://cbio.ensmp.fr/~thocking/chip-seq-chunk-db/`

- 4 annotators (AM, TDH, PGP, XJ).
- 8 cell types.
- 37 annotated H3K4me3 profiles (sharp peaks).
- 29 annotated H3K36me3 profiles (broadly enriched domains).
- 12,826 annotated regions in total.

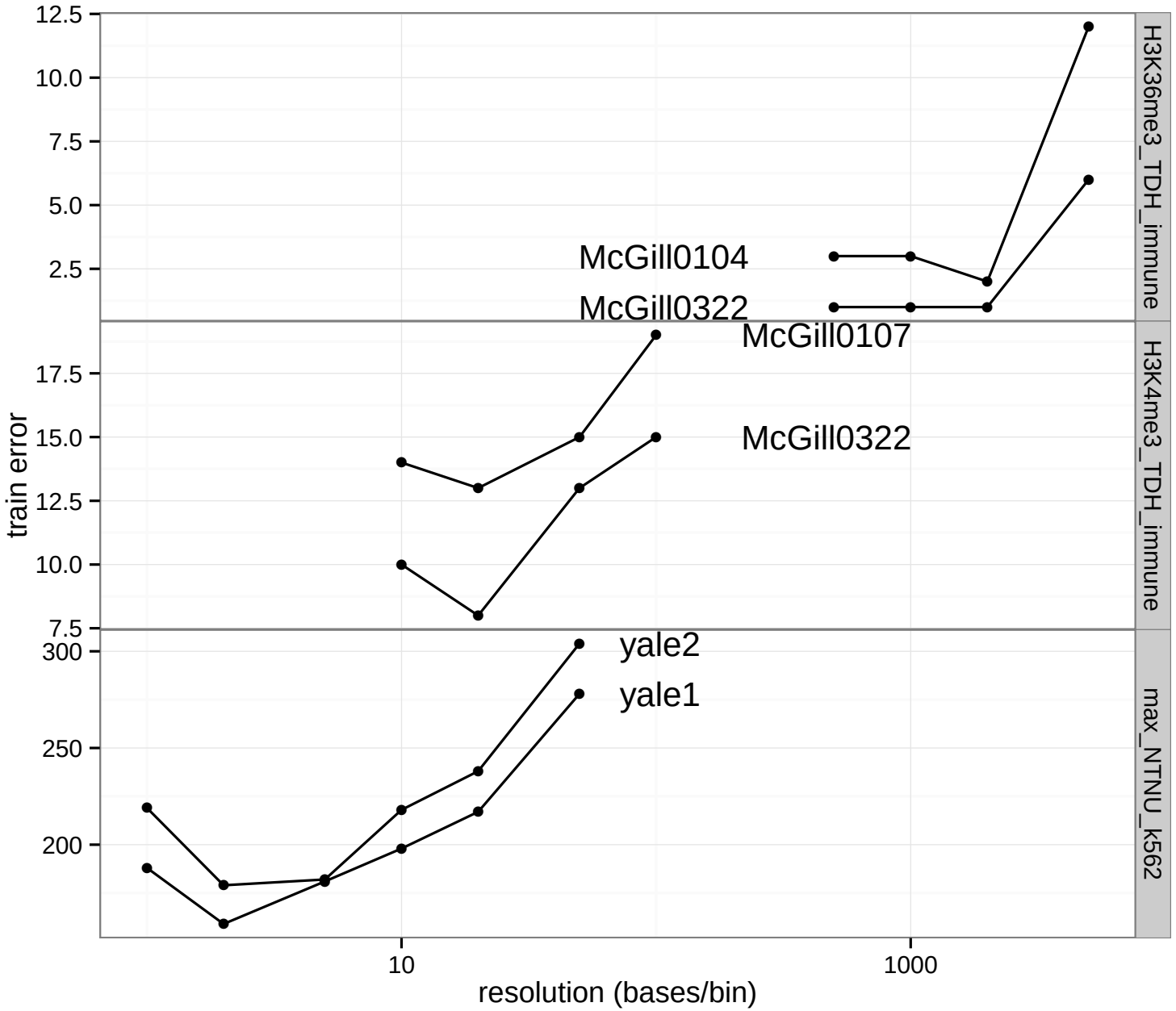
`http://cbio.ensmp.fr/~thocking/table-TF-benchmark/`

- 1 annotator.
- 3 transcription factor (TF) types: max, nrsf, srf.
- For each TF: 1 cell type, 2 replicates.

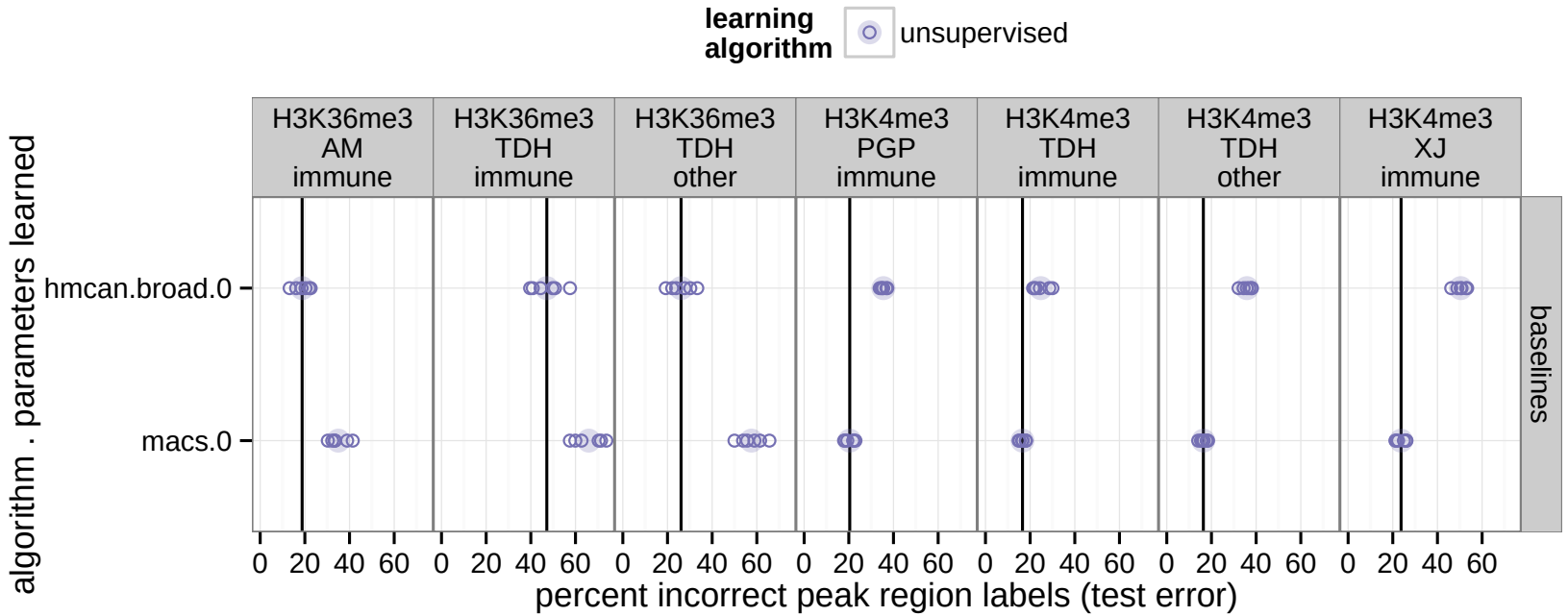
Training time proportional to number of segmentation problems



Best resolution depends on data type



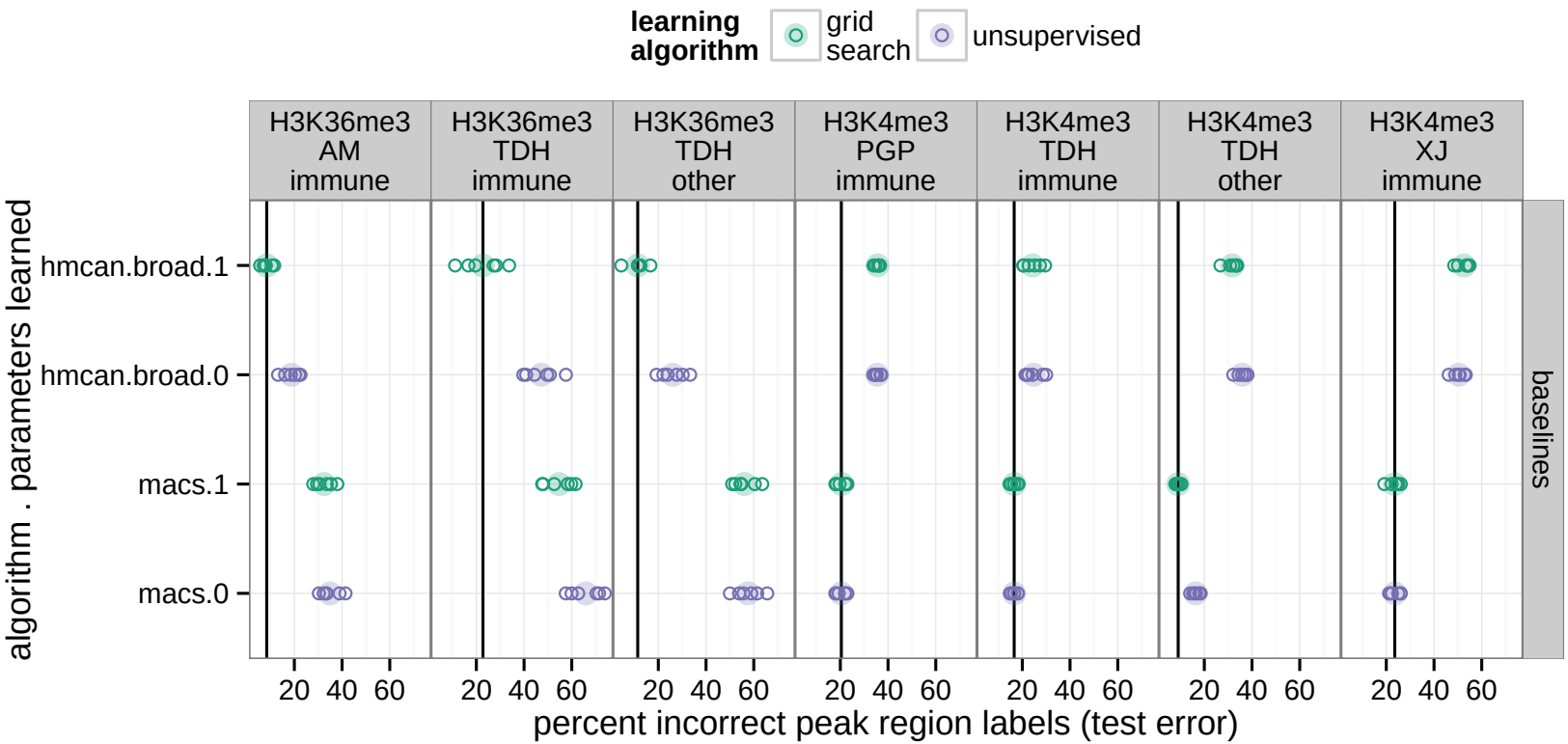
hmcan.broad better for H3K36me3, macs better for H3K4me3



Six train/test splits (open circles) and mean (shaded circle).

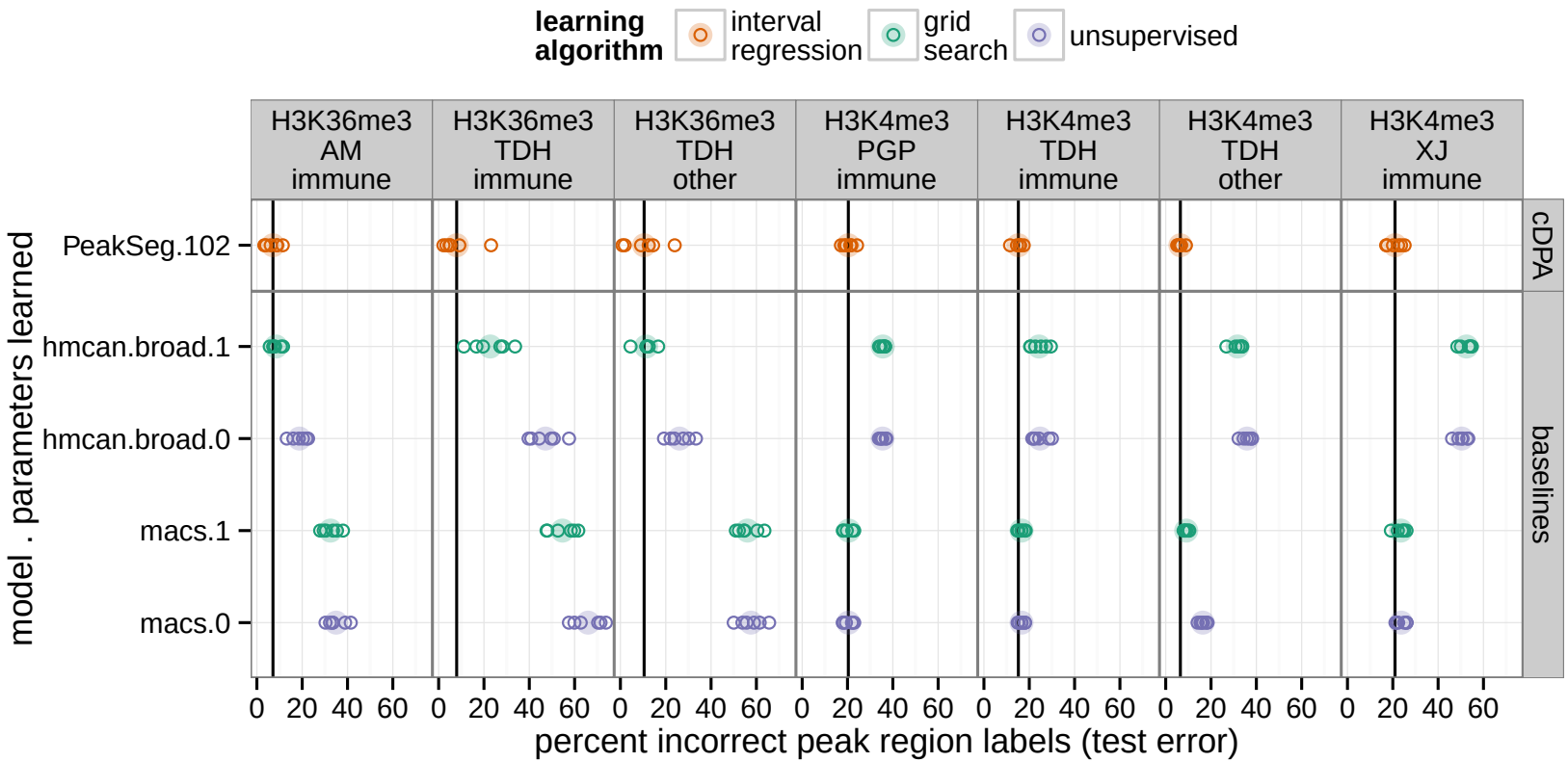
Training 1 parameter with grid search reduces test error

...except for macs, good defaults for 3/4 H3K4me3 data sets.



Six train/test splits (open circles) and mean (shaded circle).

Supervised genome-wide PeakSeg method works for both data types



Six train/test splits (open circles) and mean (shaded circle).

Conclusions and future work

PeakSeg: **Peak** detection via constrained optimal **Seg**mentation.

- Inputs: annotated region `labels.bed` instead of model parameters.
- Outputs: state-of-the-art peak detection for both H3K4me3 and H3K36me3 data.

Future work:

- Interactive visual peak labeling GUI.
- Detecting the same peaks across several profiles?
- Faster algorithm via constrained version of

Time	Models	Algorithm	Reference
$O(s_{\max} d \log d)$	$s_{\max}$	pDPA	Rigaill 2010
$O(d \log d)$	1	FPOP	Maidstone et al. 2014

d = data points to segment, $s_{\max}$ = max segments.

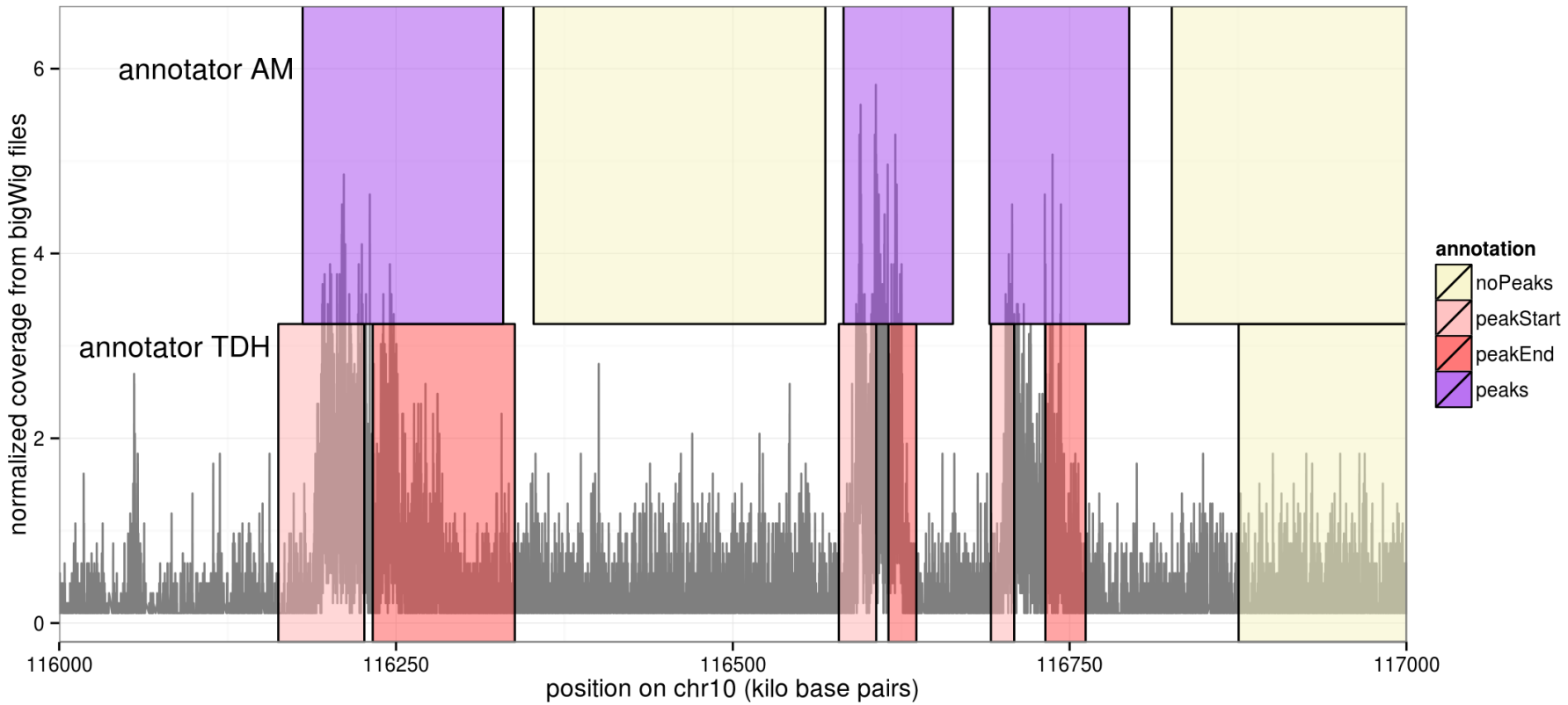
Thanks for your attention!

Write me at toby.hocking@mail.mcgill.ca to collaborate!

Source code for slides, figures, paper online!
`https://github.com/tdhock/PeakSeg-paper`

Supplementary slides appear after this one.

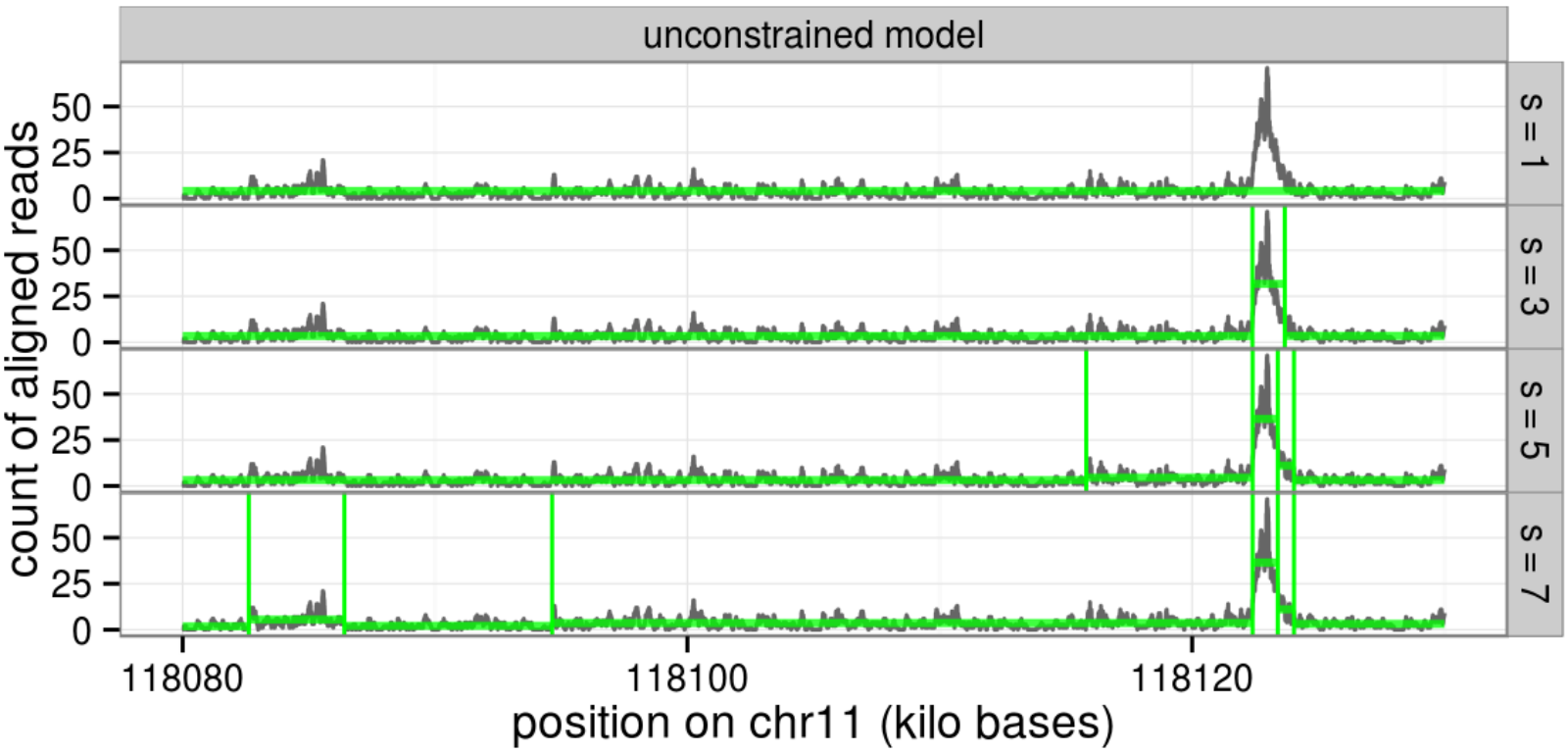
Two annotators provide consistent labels, but different precision



- TDH peakStart/peakEnd more precise than AM peaks.
- AM noPeaks more precise than TDH no label.

Maximum likelihood segmentations

For a coverage profile $\mathbf{y} \in \mathbb{Z}_+^d$, find the mean vector $\hat{\mathbf{m}}^s(\mathbf{y}) \in \mathbb{R}^d$ with maximum Poisson likelihood, given s segments ($s-1$ change-points).



Computed via Segmentor3IsBack R package (Cleynen et al. 2014)

Previous work: maximum likelihood segmentation

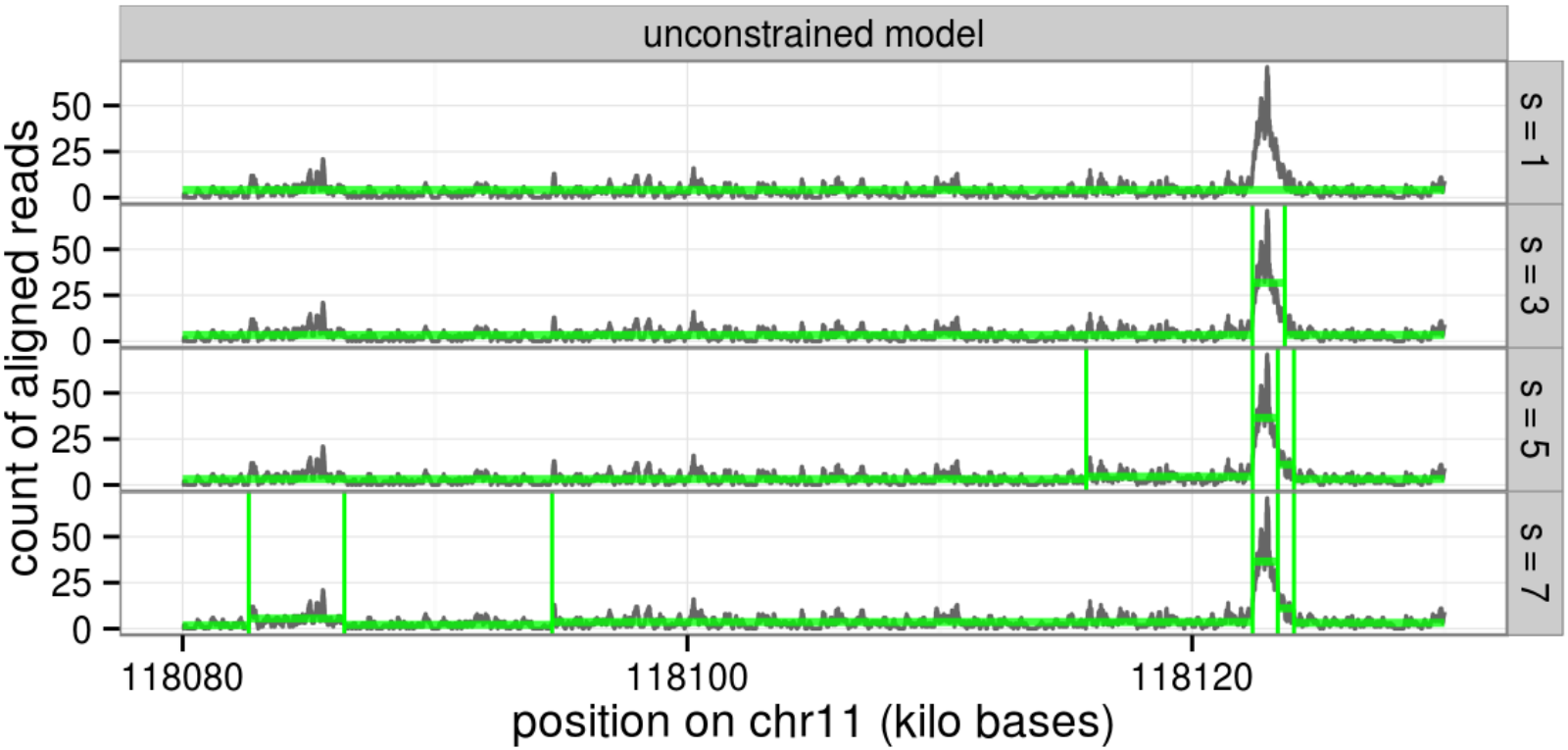
- Let $\mathbf{y} = \begin{bmatrix} y_1 & \cdots & y_d \end{bmatrix} \in \mathbb{Z}_+^d$ be the aligned read counts for one sample and one genomic region.
- Fix $s_{\max} = 19$, the maximum number of segments.
- For each number of segments $s \in \{1, \ldots, s_{\max}\}$, we want:

$$\hat{\mathbf{m}}^s(\mathbf{y}) = \underset{\mathbf{m} \in \mathbb{R}^d}{\arg\min} \sum_{j=1}^{d} m_j - y_j \log m_j \text{ (Poisson loss)}$$

$$\text{such that} \quad \text{Segments}(\mathbf{m}) = s.$$

- Pruned Dynamic Programming Algorithm = pDPA (Rigaill arXiv:1004.0887) returns $\hat{\mathbf{m}}^1(\mathbf{y}), \ldots, \hat{\mathbf{m}}^{s_{\max}}(\mathbf{y})$ in $O(s_{\max} d \log d)$ time.

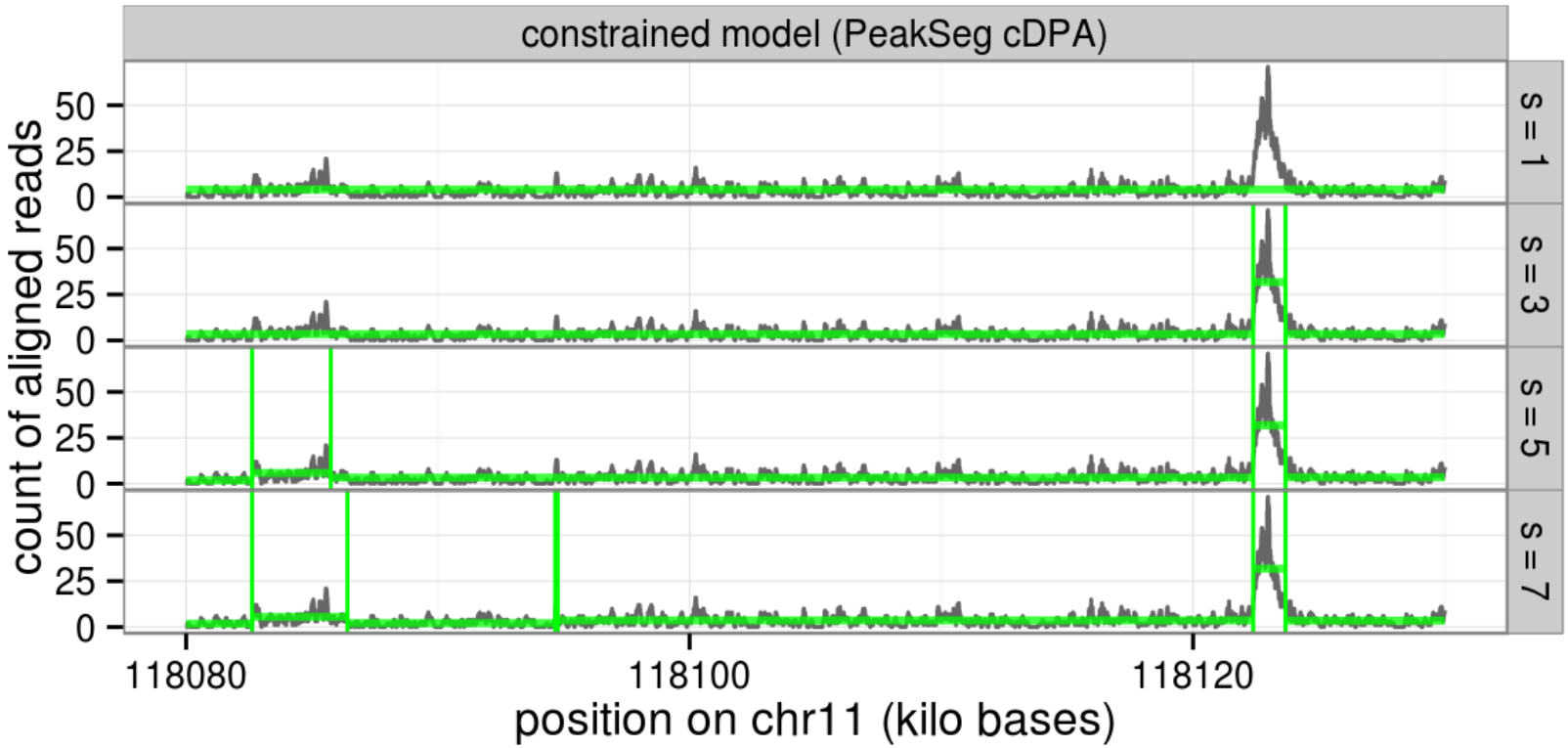
Maximum likelihood segmentations



Model with $s = 5$ segments changes up, up, down, down.

How to define peaks? Introduce a threshold parameter?

Constrained maximum likelihood segmentations



Model with $s = 5$ segments changes up, down, up, down.
Peaks are even-numbered segments.

PeakSeg: constrained maximum likelihood segmentation

For each number of segments $s \in \{1, \dots, s_{\max}\}$, we want:

$$\begin{aligned} \tilde{\mathbf{m}}^s(\mathbf{y}) = \arg\min_{\mathbf{m} \in \mathbb{R}^d} & \quad \sum_{j=1}^{d} m_j - y_j \log m_j \\ \text{such that} & \quad \text{Segments}(\mathbf{m}) = s, \\ \forall j \in \{1, \dots, d\}, & \quad P_j(\mathbf{m}) \in \{0, 1\}. \end{aligned}$$

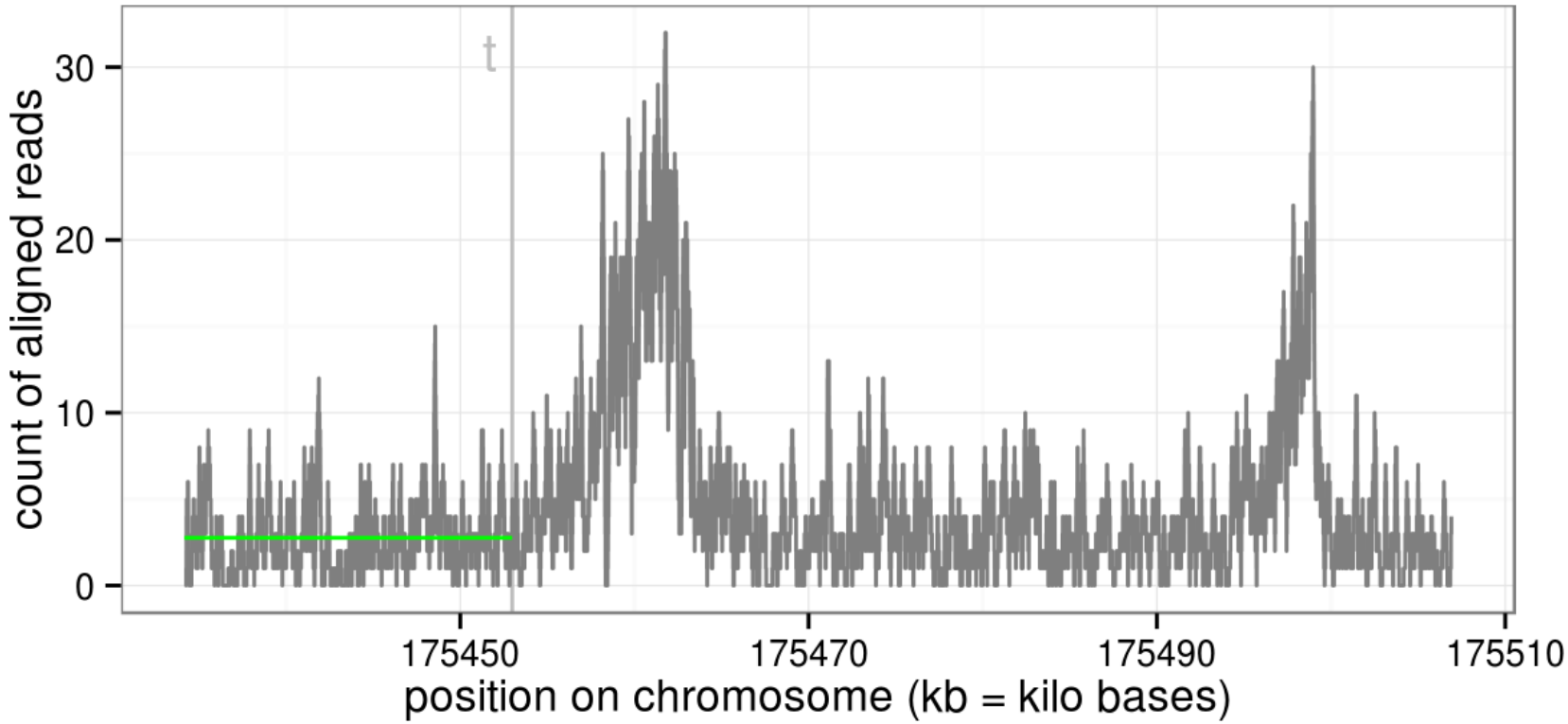
up, down, up, down constraint.

where the peak indicator $P_1(\mathbf{m}) = 0$ and for $j > 1$,

$$P_j(\mathbf{m}) = \sum_{k=2}^{j} \text{sign}(m_k - m_{k-1}).$$

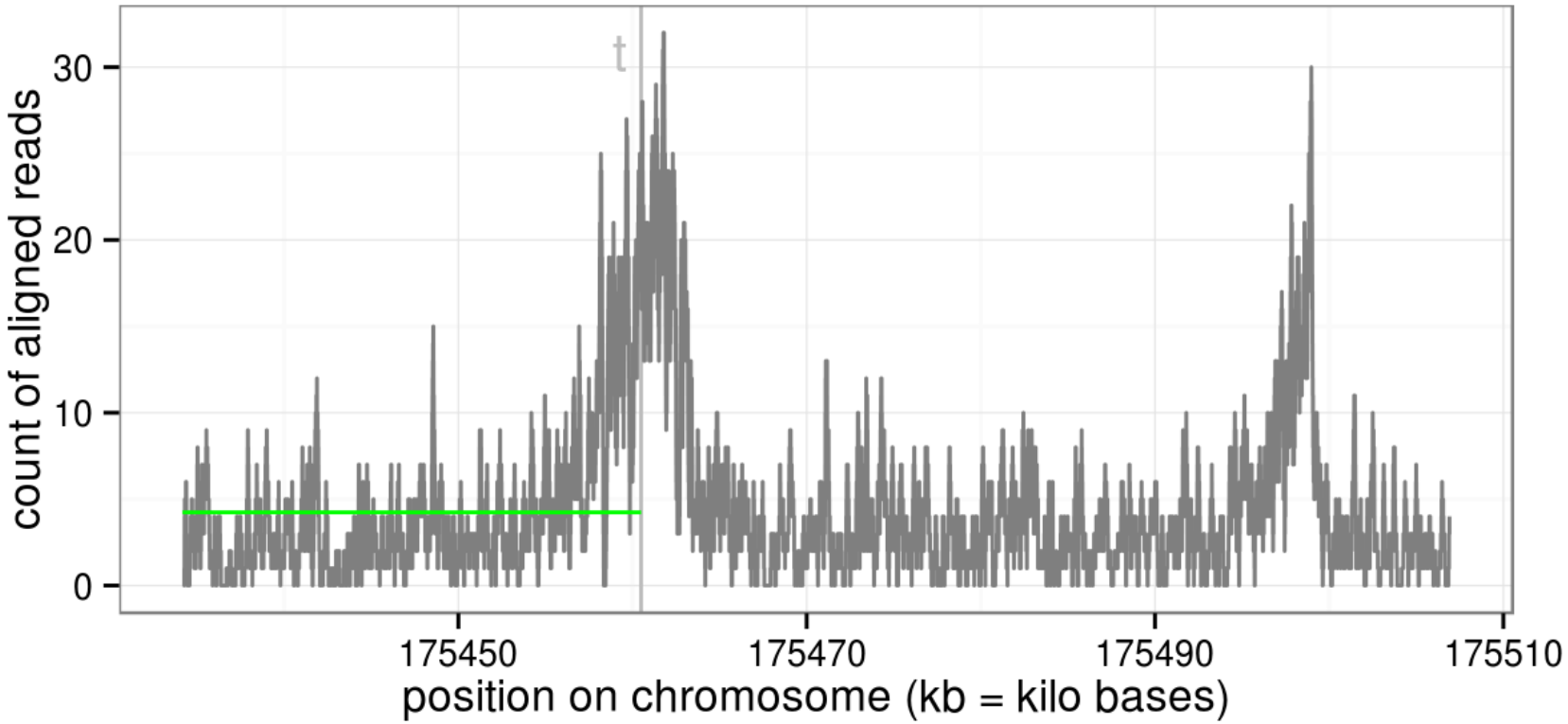
We propose cDPA = a constrained dynamic programming algorithm, which computes $s_{\max}$ models in $O(s_{\max} d^2)$ time.

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 1$ segments up to data point t



$$\mathcal{L}_{1,t} = \underbrace{c_{(0,t]}}_{\text{optimal loss of 1st segment } (0,t]}$$

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 1$ segments up to data point t



$$\mathcal{L}_{1,t} = \underbrace{c_{(0,t]}}_{\text{optimal loss of 1st segment } (0,t]}$$

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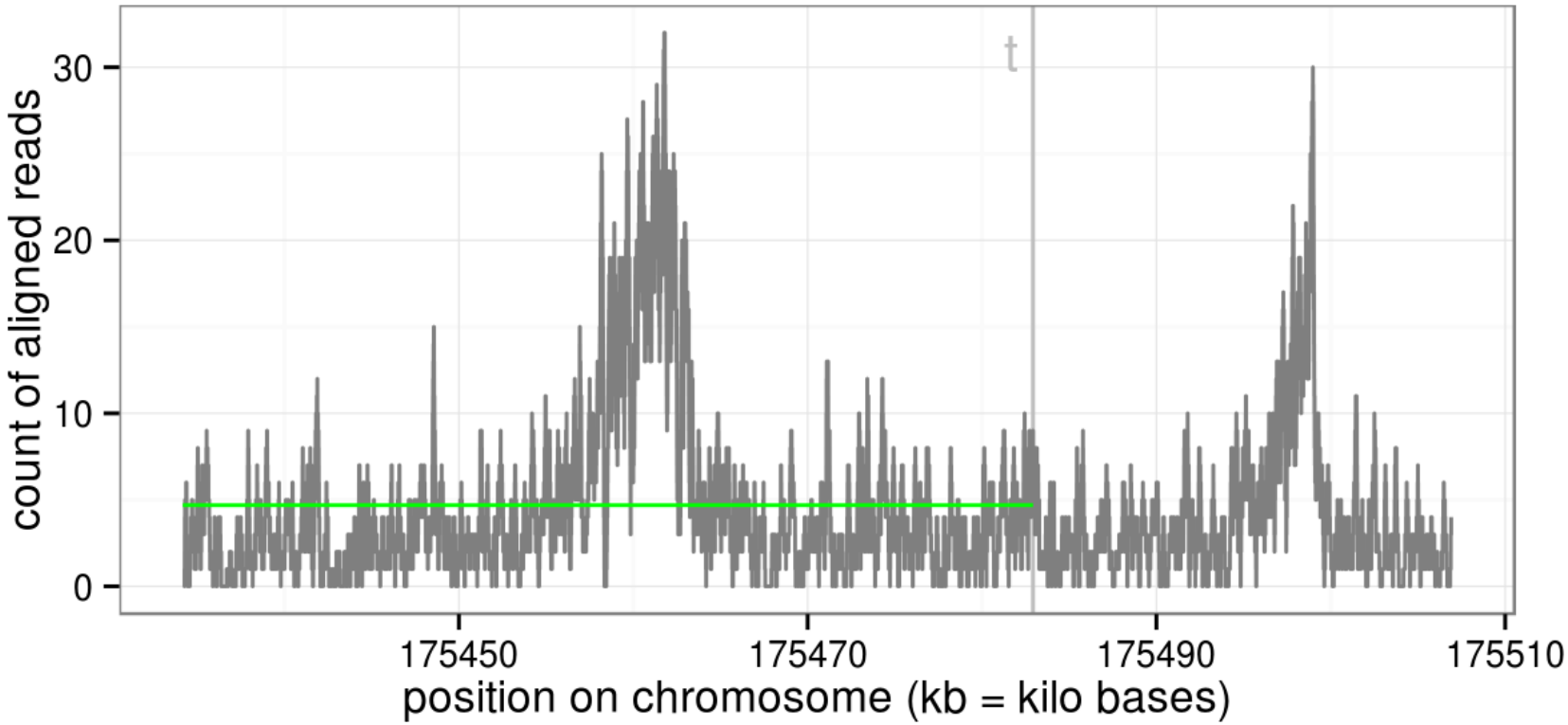
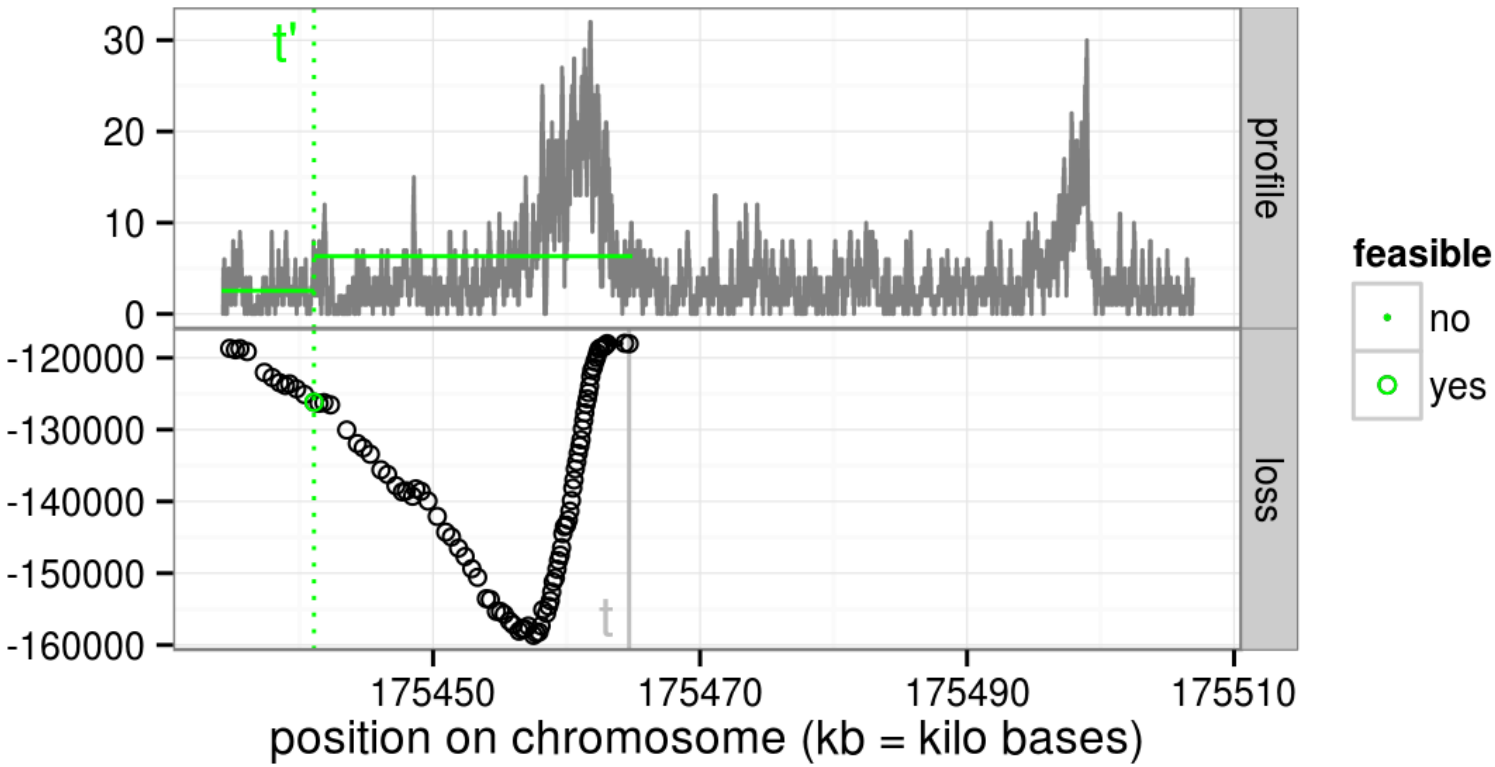


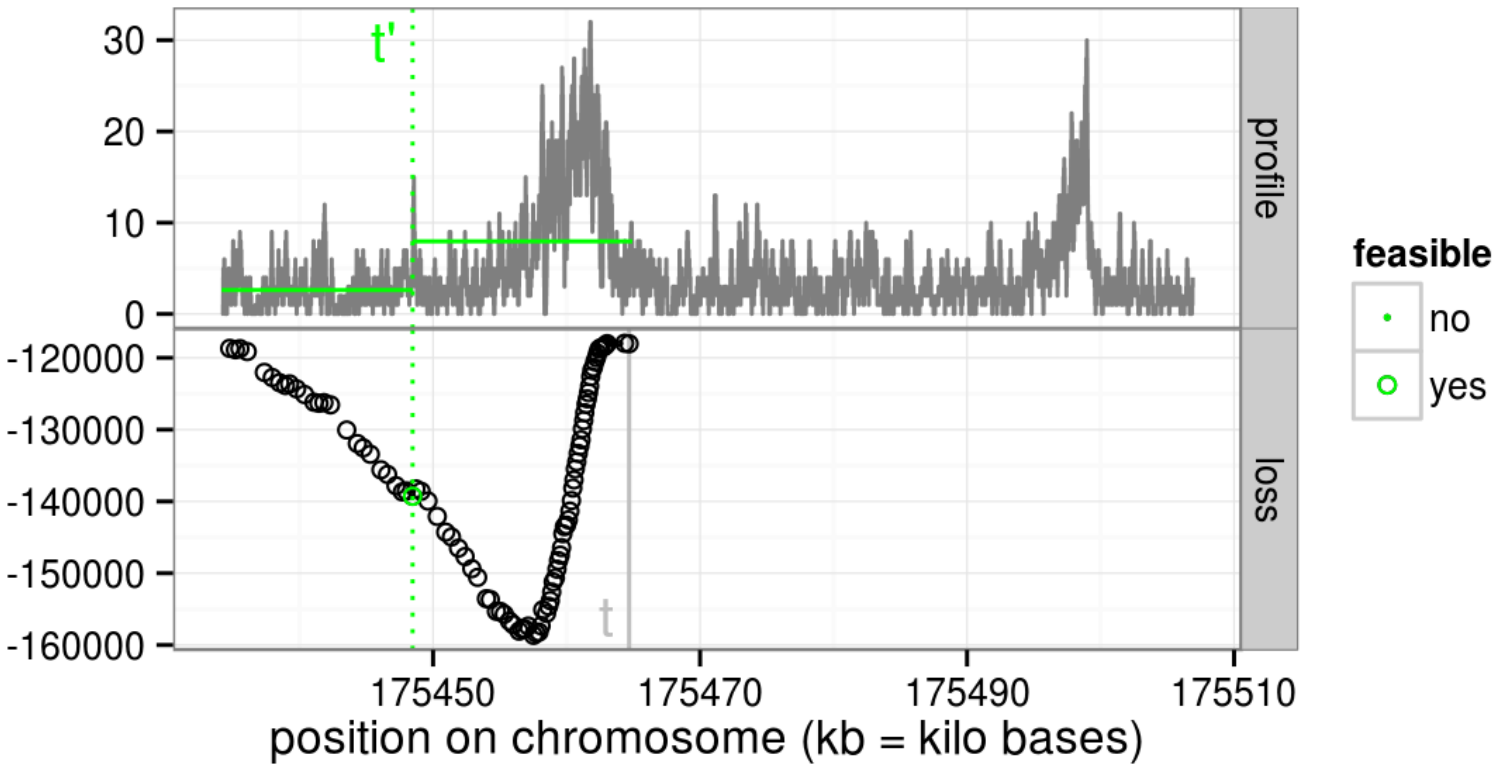
$$\mathcal{L}_{1,t} = \underbrace{c_{(0,t]}}_{\text{optimal loss of 1st segment } (0,t]}$$

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 2$ segments up to data point $t < d$



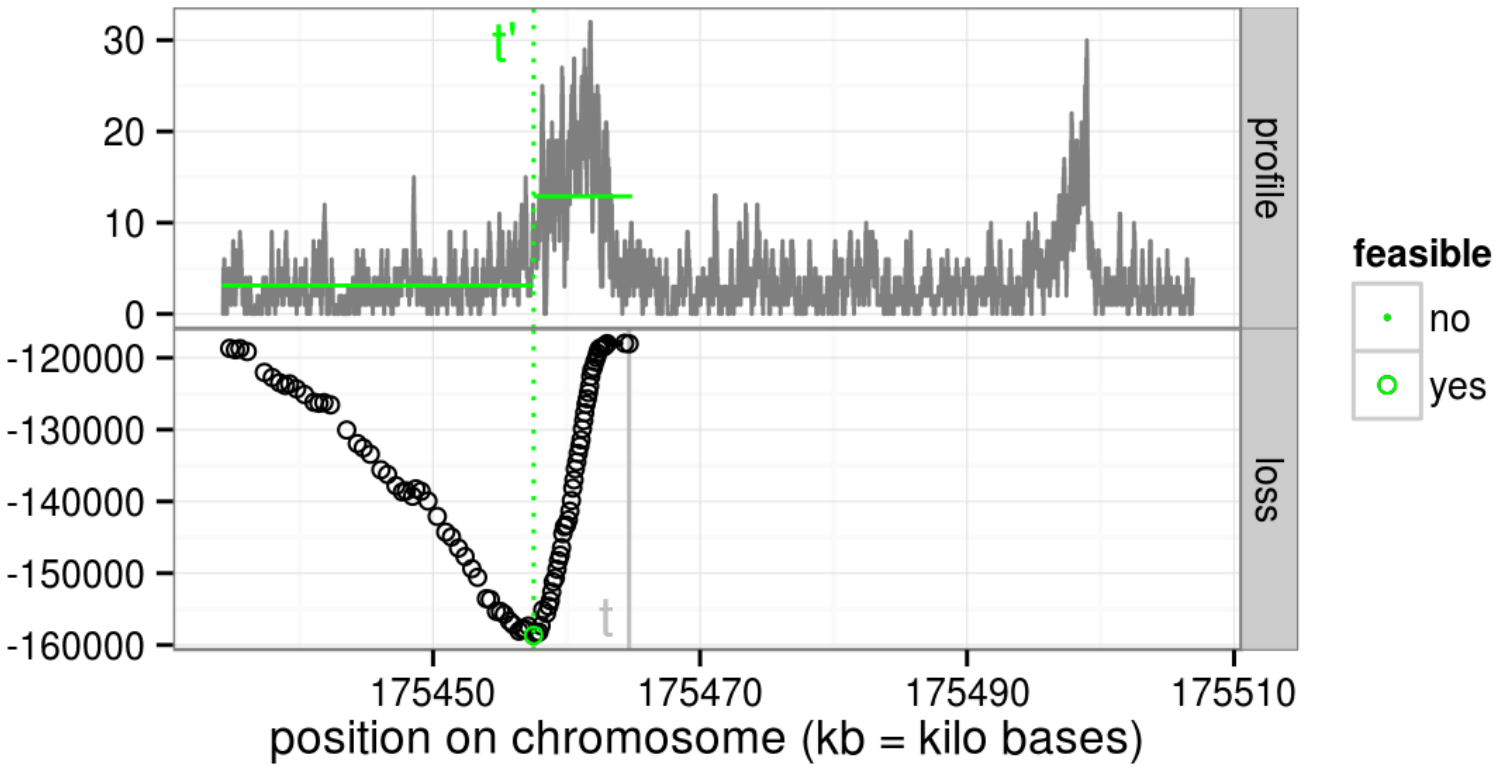
$$\mathcal{L}_{2,t} = \min_{t'<t} \underbrace{\mathcal{L}_{1,t'}}_{\text{optimal loss in 1 segment up to } t'} + \underbrace{c_{(t',t]}}_{\text{optimal loss of 2nd segment } (t',t]}$$

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 2$ segments up to data point $t < d$



$$\mathcal{L}_{2,t} = \min_{t'<t} \underbrace{\mathcal{L}_{1,t'}}_{\text{optimal loss in 1 segment up to } t'} + \underbrace{c_{(t',t]}}_{\text{optimal loss of 2nd segment } (t',t]}$$

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 2$ segments up to data point $t < d$



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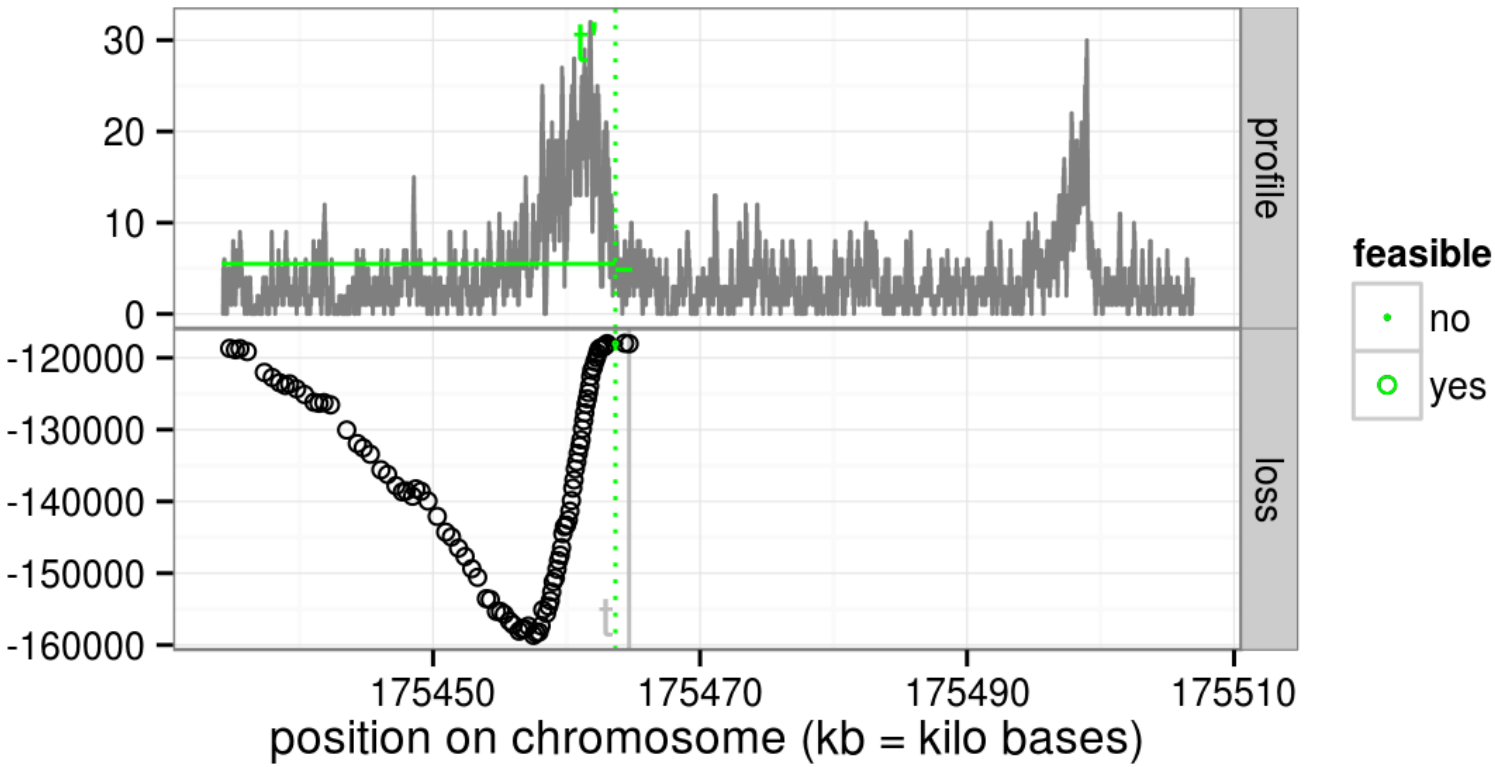

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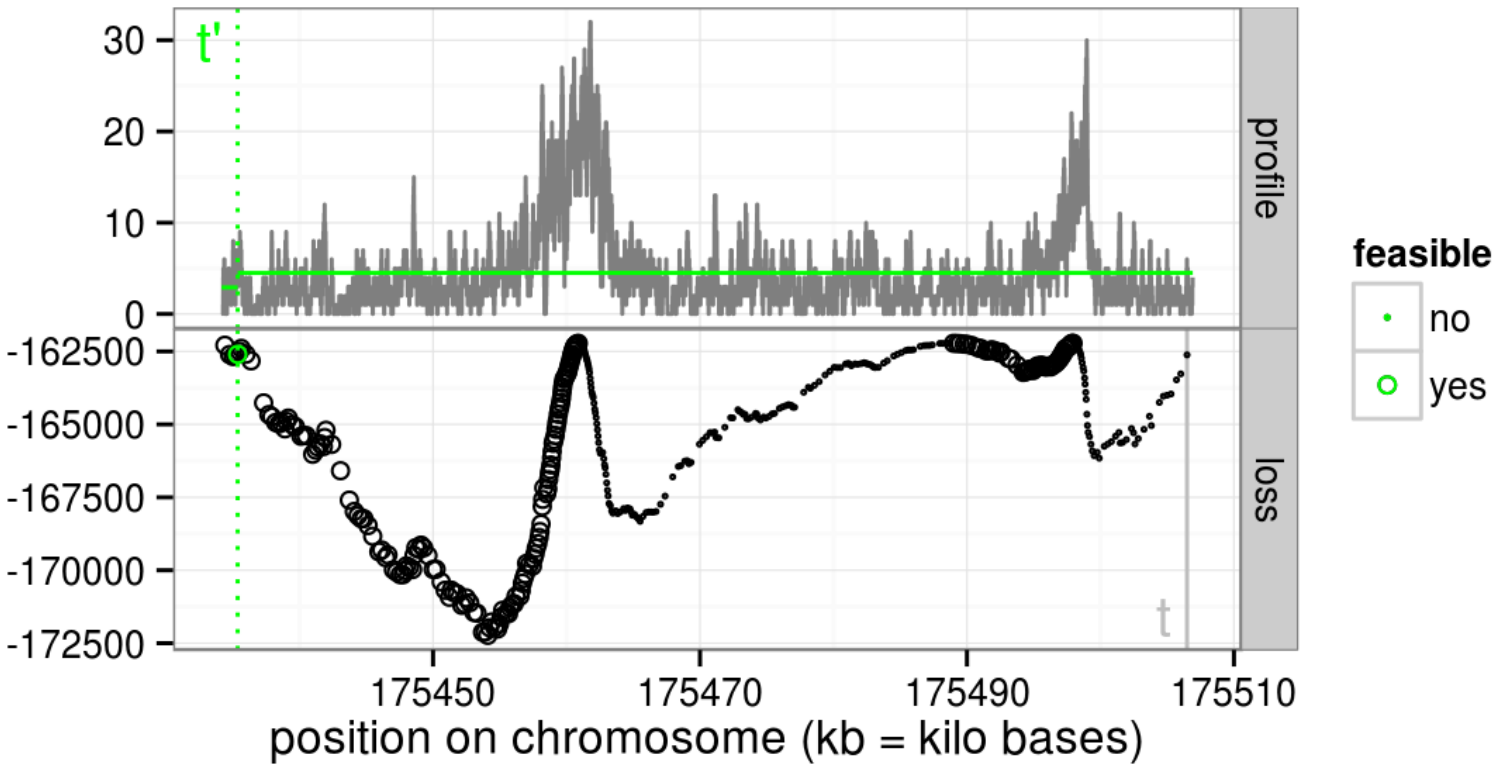

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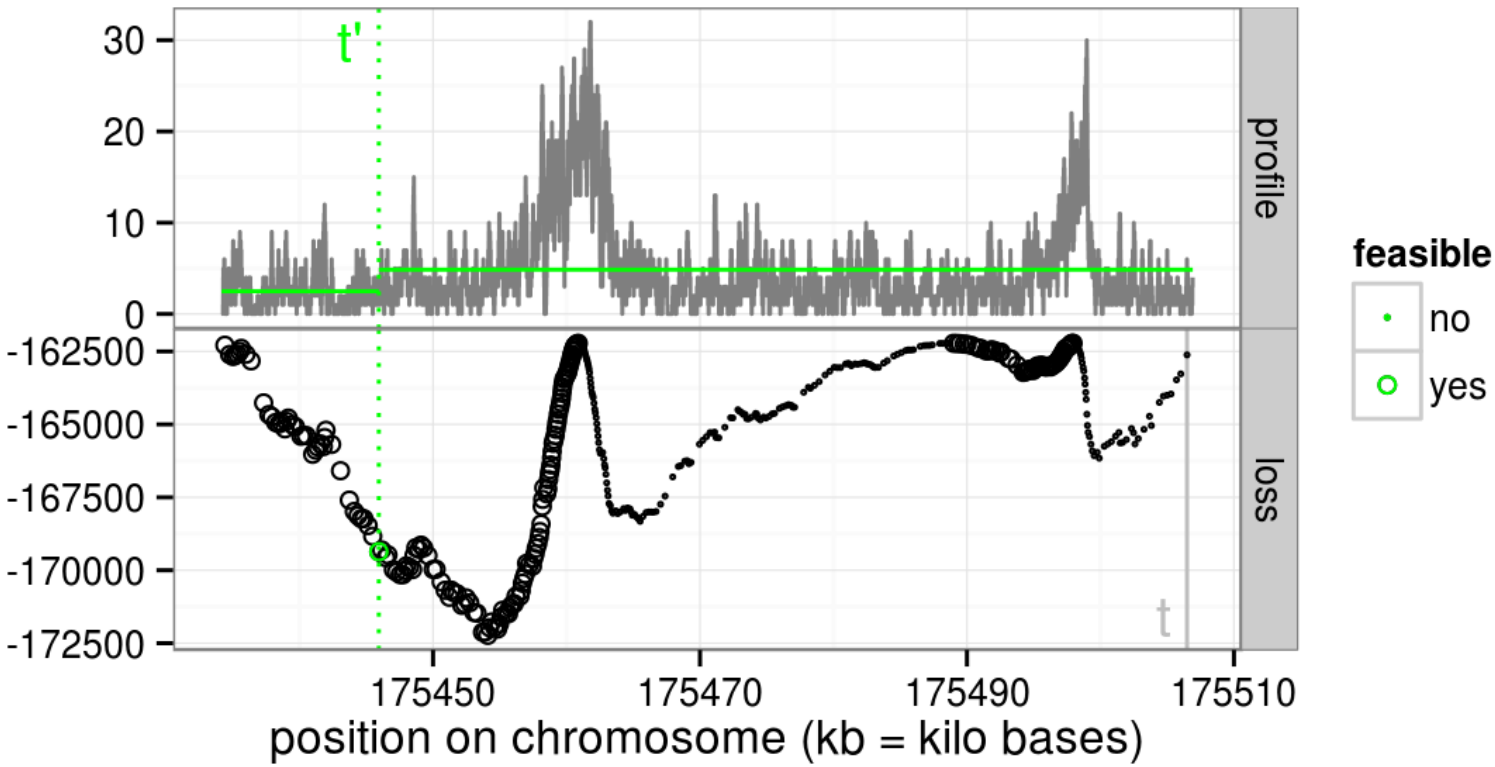

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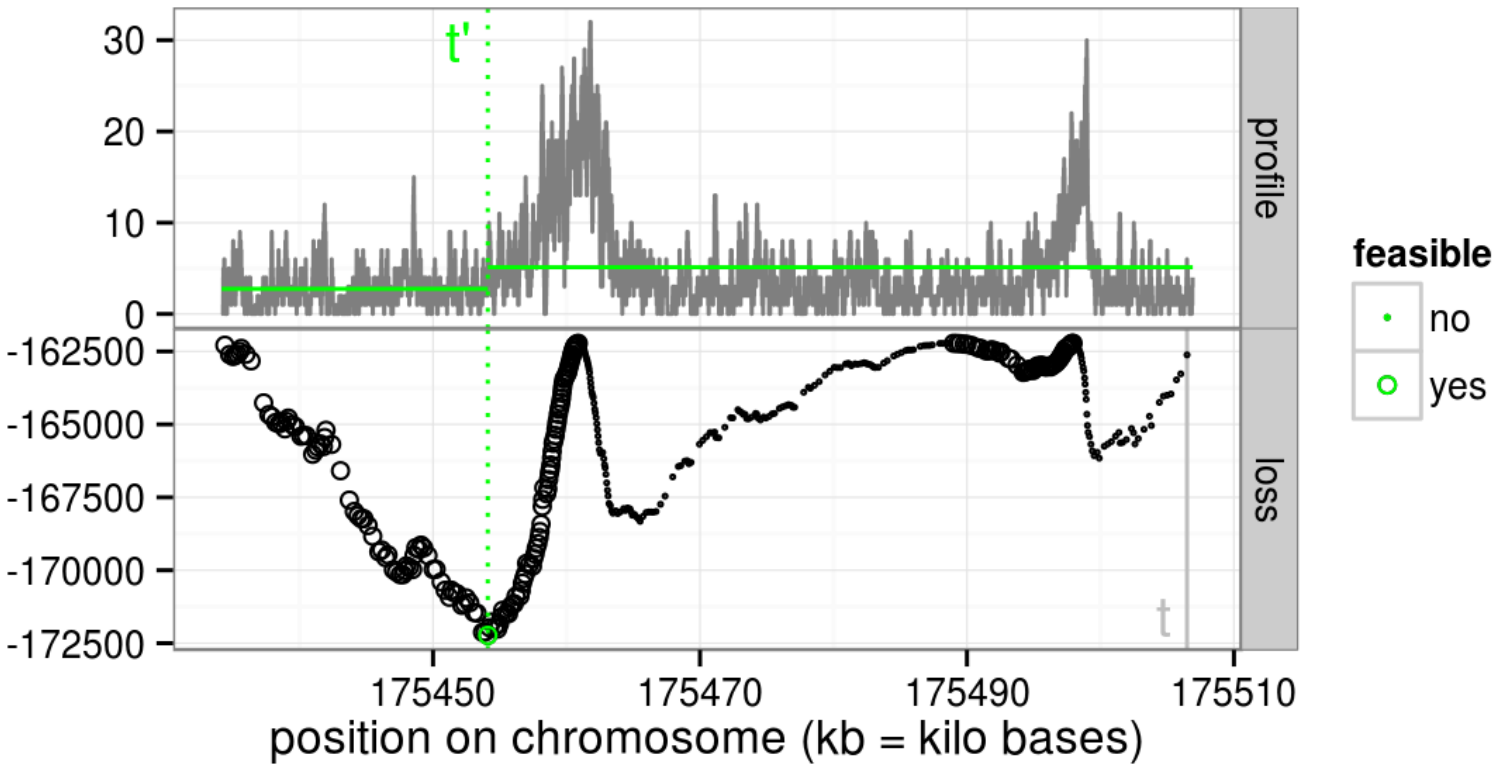

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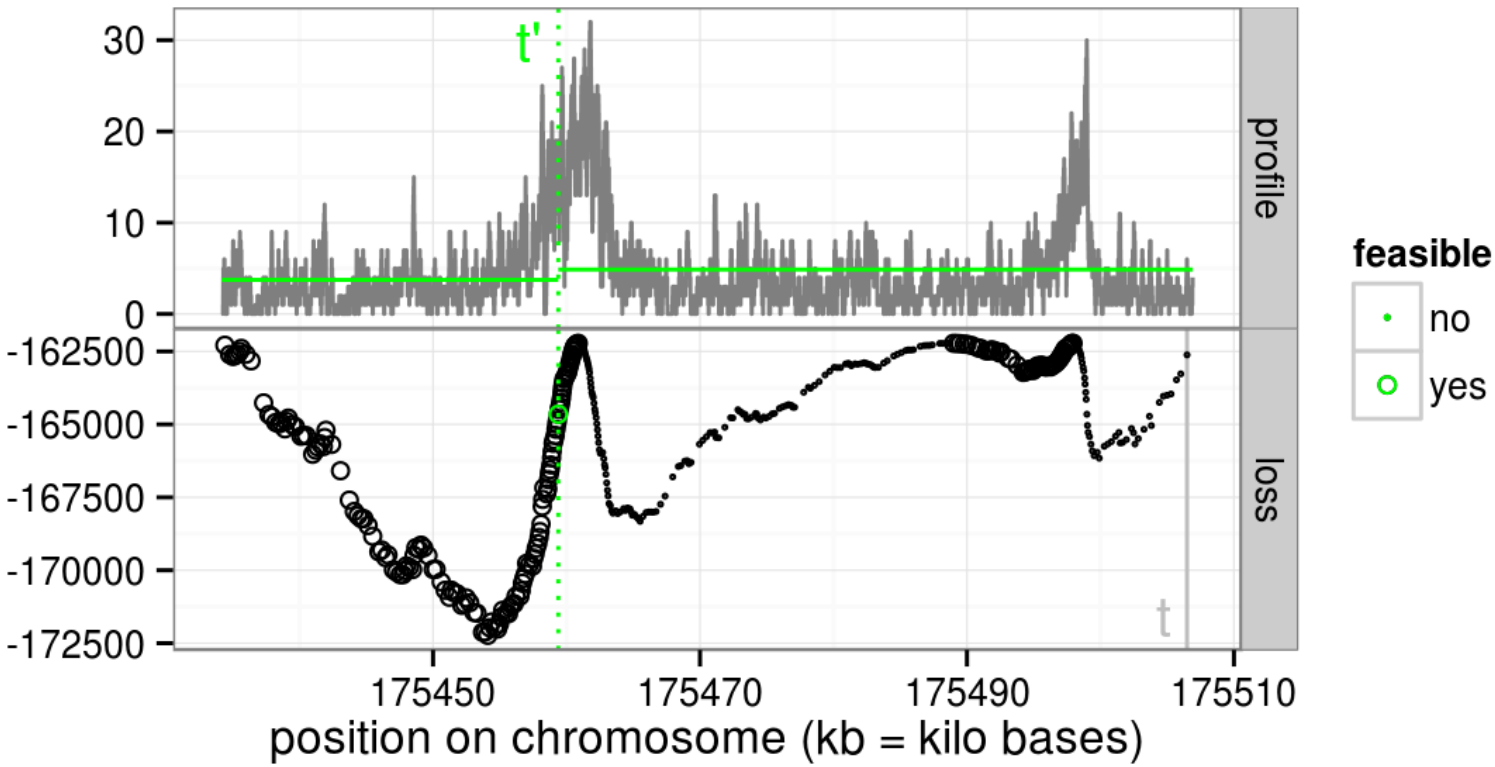

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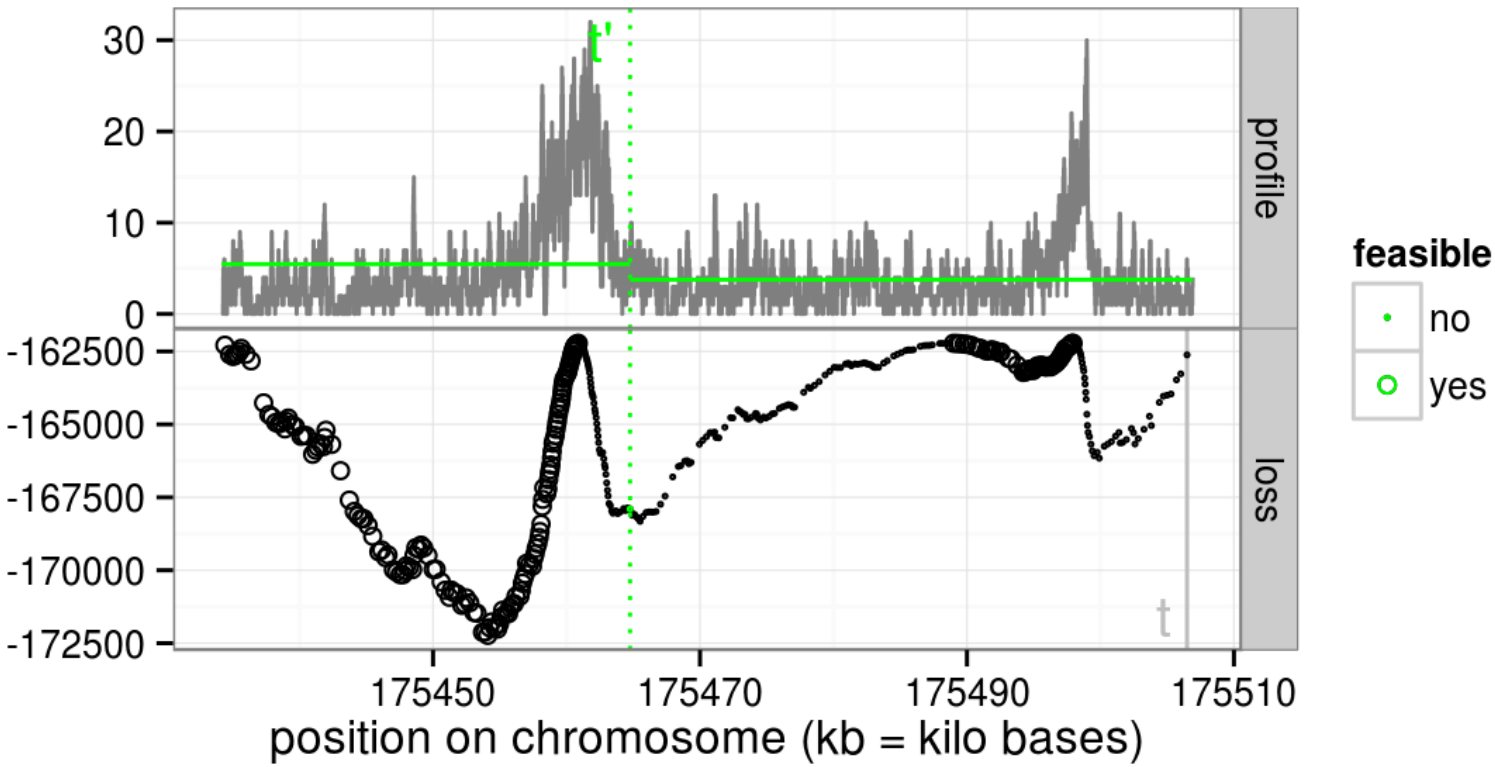

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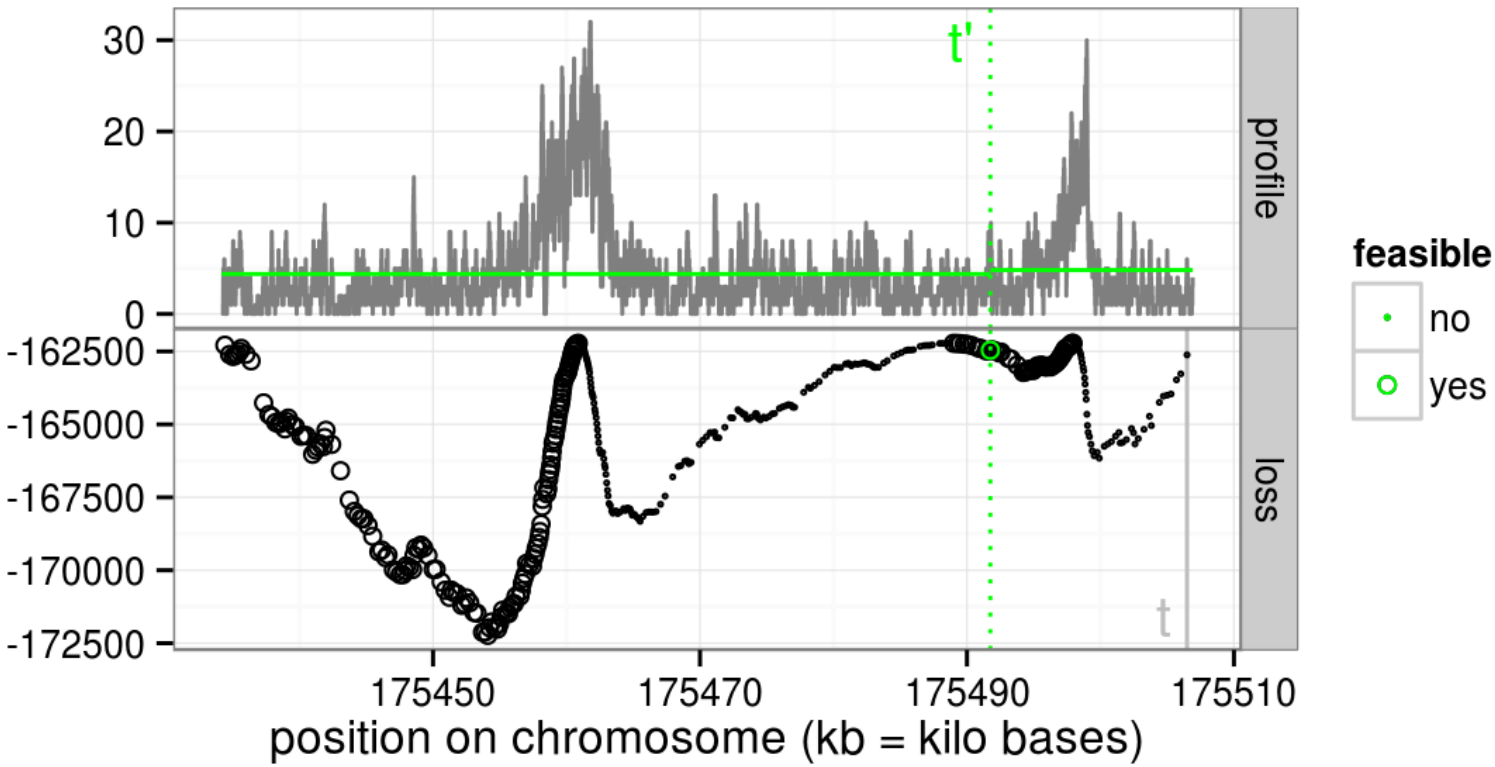

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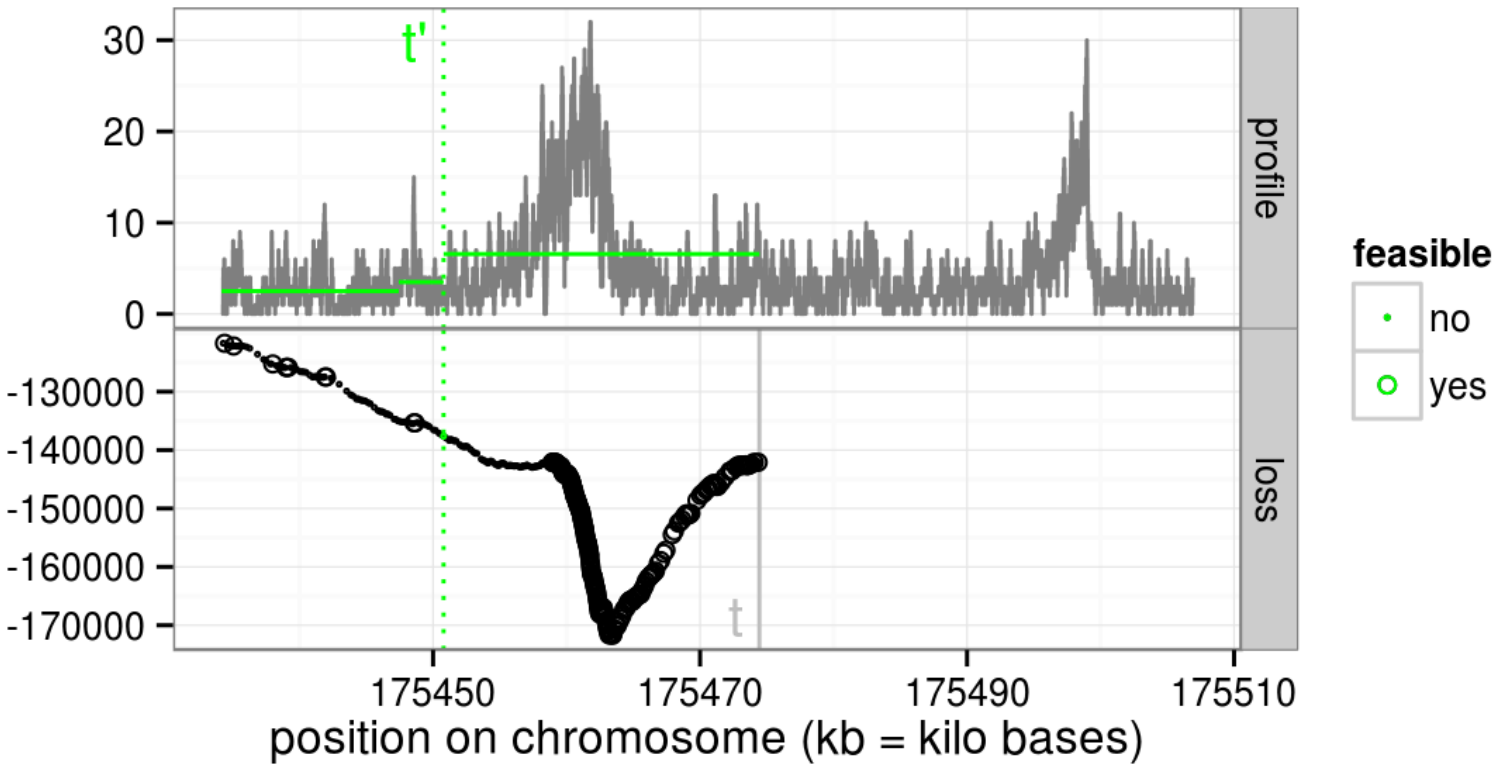
Dynamic programming is faster than grid search for $s > 2$ segments

Computation time in number of data points d:

segments s	grid search	dynamic programming
1	$O(d)$	$O(d)$
2	$O(d^2)$	$O(d^2)$
3	$O(d^3)$	$O(d^2)$
4	$O(d^4)$	$O(d^2)$
$\vdots$	$\vdots$	$\vdots$

For example $d = 5735$ data points to segment.
$d^2 = 32890225$
$d^3 = 188625440375$
$\vdots$

Computation of optimal loss $\mathcal{L}_{s,t}$ for $s = 3$ segments up to data point t



$$\mathcal{L}_{3,t} = \min_{t'<t} \underbrace{\mathcal{L}_{2,t'}}_{\text{optimal loss in 2 segments up to } t'} + \underbrace{c_{(t',t]}}_{\text{optimal loss of 3rd segment } (t',t]}$$

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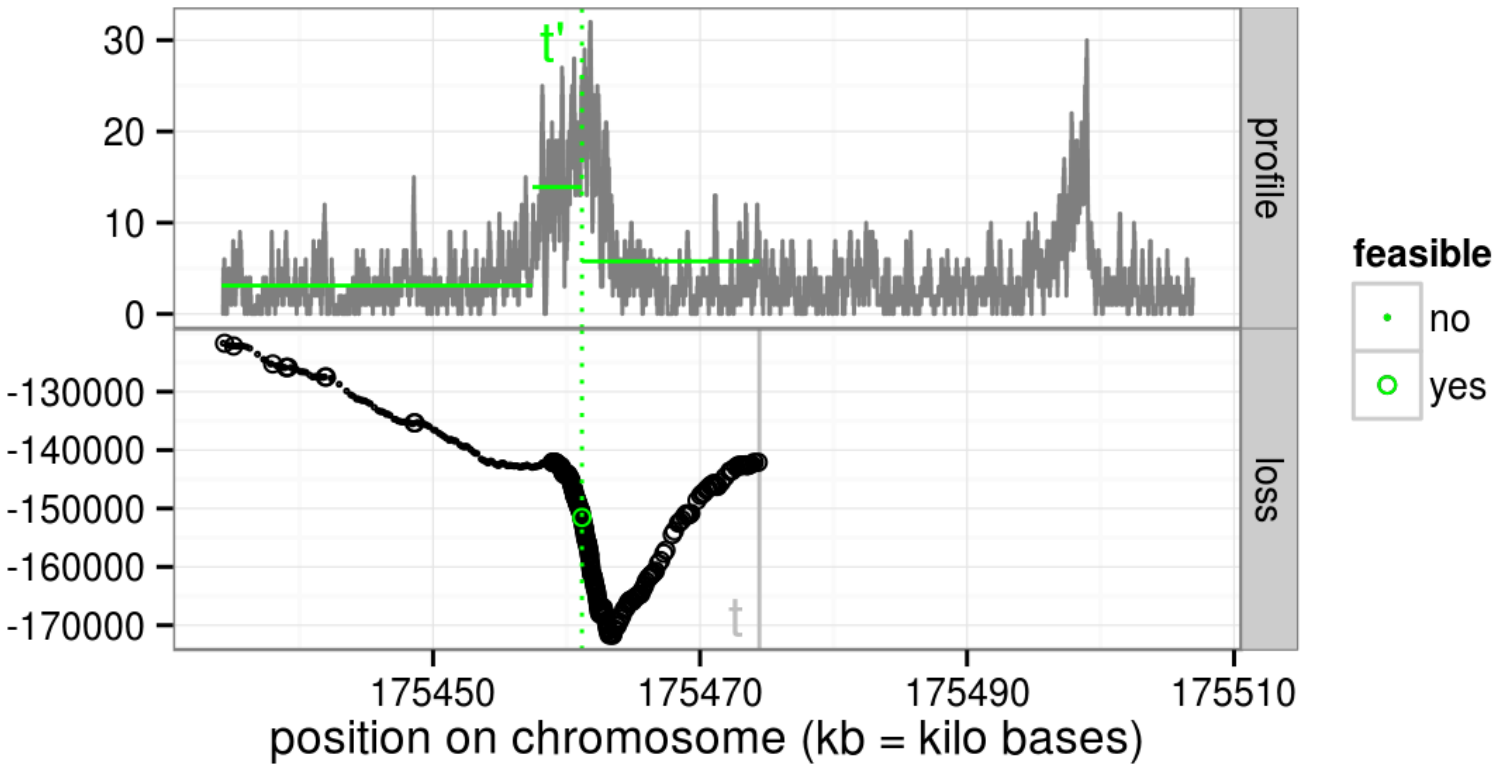

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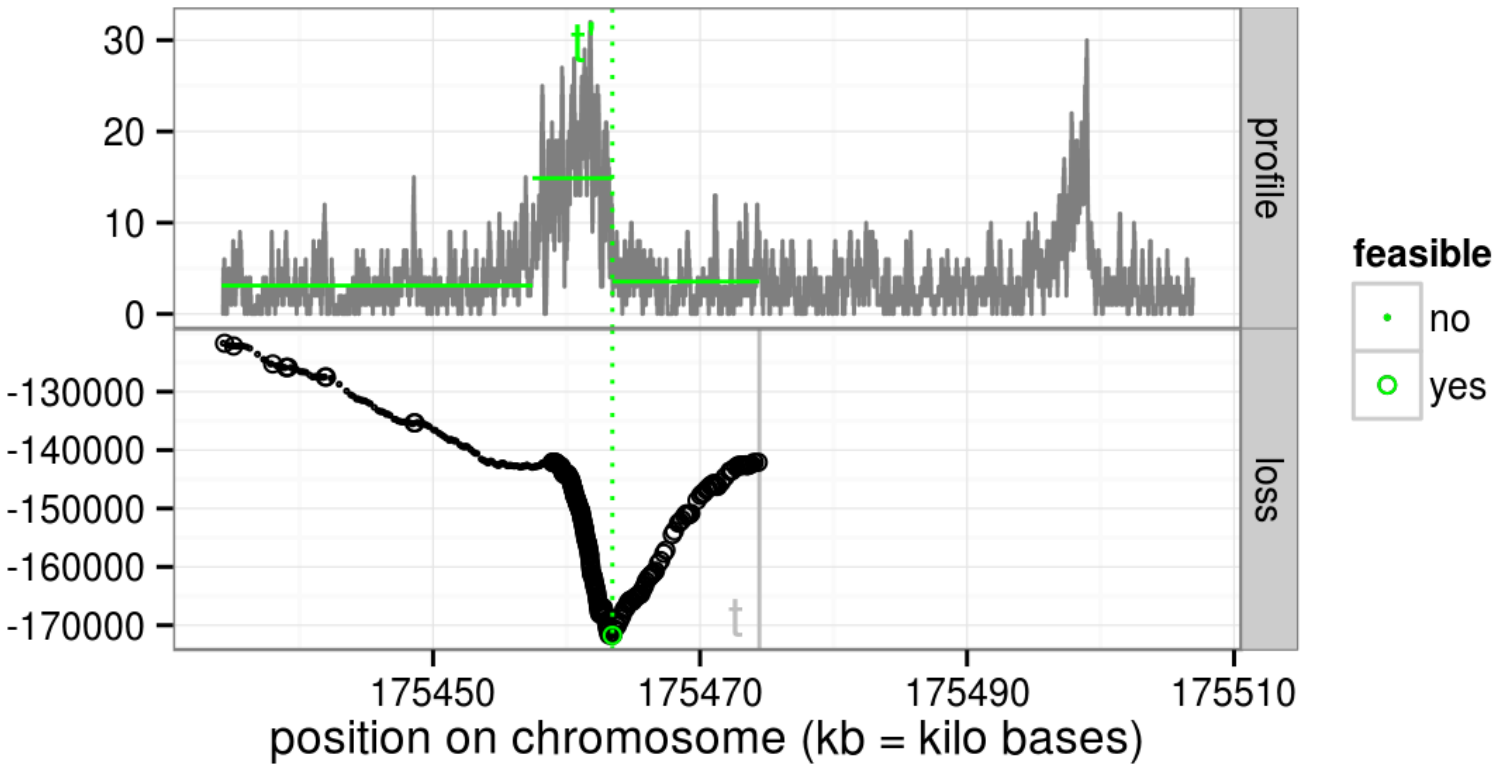

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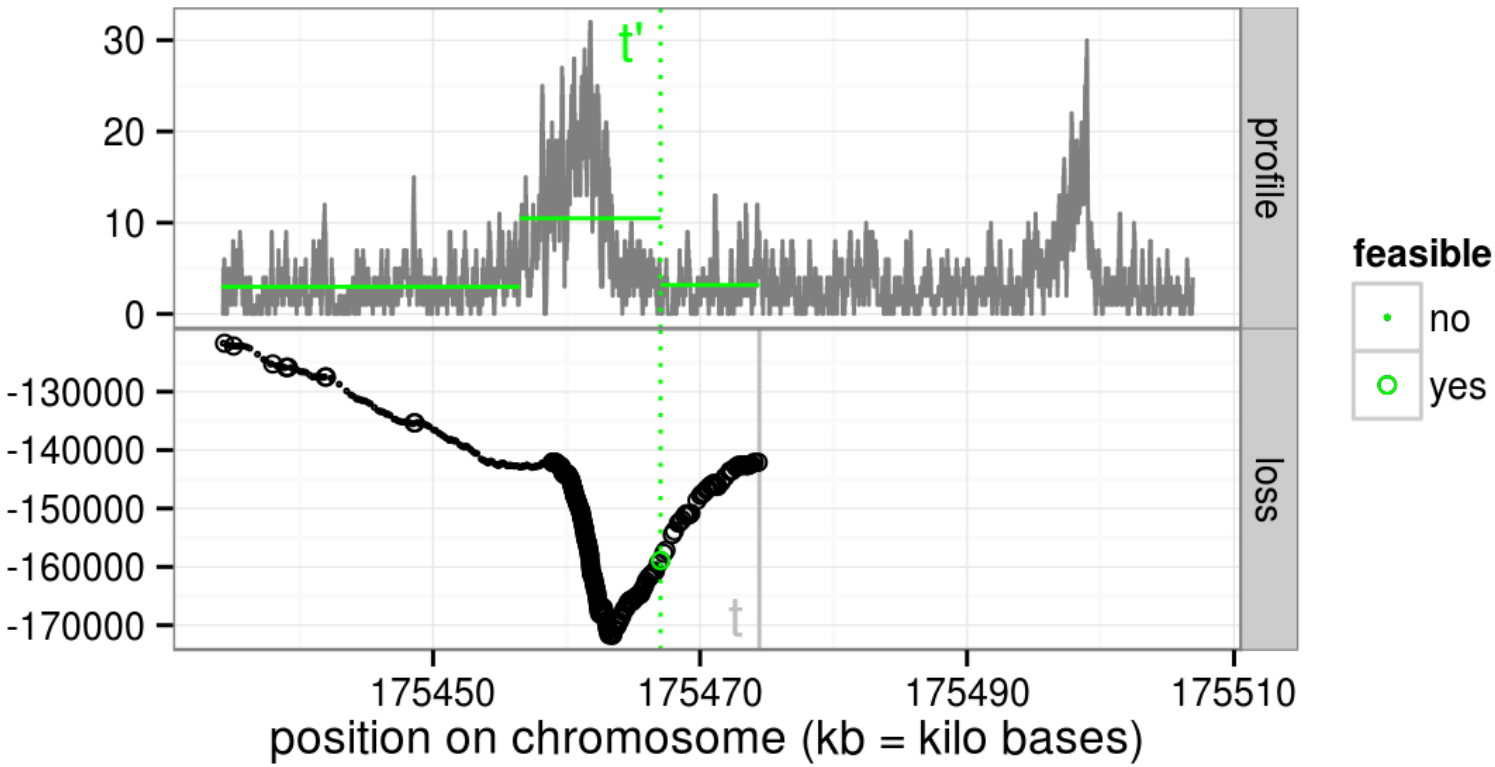

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Step 1: compute annotation error functions

- Inputs: for $i \in \{1, \ldots, n\}$ samples, genomic profiles $\mathbf{y}_i$, annotated regions R_i.

	0 peaks	$\cdots$	$p_{\max}$ peaks
segmentations	$\tilde{\mathbf{m}}^0(\mathbf{y}_i)$	$\cdots$	$\tilde{\mathbf{m}}^{p_{\max}}(\mathbf{y}_i)$
annotation error	$e_i(0)$	$\cdots$	$e_i(p_{\max})$

- R package `https://github.com/tdhock/PeakError/` computes the **annotation error** $e_i : \{0, \ldots, p_{\max}\} \to \mathbb{Z}_+$.
- TD Hocking *et al.* Visual annotations and a supervised learning approach for evaluating and calibrating ChIP-seq peak detectors (arXiv:1409.6209).

Step 2: compute model selection functions

For each sample/chromosome $i \in \{1, \ldots, n\}$, for $\lambda \in \mathbb{R}_+$,

- The **optimal number of peaks** function is

$$p_i^*(\lambda) = \underset{p \in \{1,\ldots,p_{\max}\}}{\arg\min} \alpha_i^p + \lambda p,$$

  where α_i^p is the Poisson loss of the model with p peaks.

- The **penalized annotation error** function is

$$E_i(\lambda) = e_i\left[p_i^*(\lambda)\right],$$

  where $e_i(p)$ is the number of incorrect annotations for the model with p peaks.

Peaks p_i^* and error E_i are non-convex, piecewise constant functions that can be computed exactly.

Step 3: learn a penalty function via interval regression

- Compute the target interval $(\underline{L}_i, \overline{L}_i)$.
- $\log \lambda_i \in (\underline{L}_i, \overline{L}_i) \Rightarrow$ optimal peak detection.
- Compute simple features $\mathbf{x}_i \in \mathbb{R}^m$, e.g. chromosome size, read counts, signal scale $\log \max \mathbf{y}_i$.
- Learn an optimal affine $f(\mathbf{x}_i) = \beta + \mathbf{w}^\intercal \mathbf{x}_i = \log \lambda_i$.
- Equivalent to learning a penalty $\lambda_i = \exp f(\mathbf{x}_i)$:

$$\begin{aligned} p_i^*[\exp f(\mathbf{x}_i)] &= \arg\min_p \alpha_i^p + p \exp f(\mathbf{x}_i) \\ &= \arg\min_p \alpha_i^p + p(\max \mathbf{y}_i)^w e^\beta. \end{aligned}$$

- Convex optimization problem, global optimum, variable selection (G Rigaill, TD Hocking, *et al.* ICML 2013).

Summary of supervised PeakSeg algorithm

- Fix the maximum number of peaks $p_{\max} = 10,000$.
- For each sample/chromosome $i \in \{1, \ldots, n\}$,
  - **Unsupervised PeakSeg**: compute constrained maximum likelihood segmentations $\tilde{\mathbf{m}}^0(\mathbf{y}_i), \ldots, \tilde{\mathbf{m}}^{p_{\max}}(\mathbf{y}_i)$.
  - Step 1: use annotated region labels to compute the annotation error $e_i(0), \ldots, e_i(p_{\max})$.
  - Step 2: compute peaks $p_i^*(\lambda)$, error $E_i(\lambda)$, and target interval $(\underline{L}_i, \overline{L}_i)$.
- Step 3: learn a penalty $\lambda_i = \exp f(\mathbf{x}_i)$ using features $\mathbf{x}_i$ such as $\log \max(\mathbf{y}_i)$.
- Given an unlabeled chromosome $(\mathbf{x}, \mathbf{y})$, we predict $\tilde{\mathbf{m}}^{p^*[\exp f(\mathbf{x})]}(\mathbf{y})$.

Penalty functions learned in this paper

Predicted number of segments for profile $i \in \{1, \ldots, n\}$:

$$\hat{s}_i = \underset{s \in \{1,3,\ldots,s_{\max}=19\}}{\arg\min} \overbrace{\rho\left[\tilde{\mathbf{m}}^s(\mathbf{y}_i), \mathbf{y}_i\right]}^{\text{Poisson loss}} + \overbrace{h(s, d_i)\lambda_i}^{\text{penalty}},$$

Names: (model complexity).(number of parameters learned):

name	**model complexity** $h(s, d_i)$
AIC/BIC.*	s
oracle.*	$s\left(1 + 4\sqrt{1.1 + \log(d_i/s)}\right)^2$

name	**smoothing** λ_i	**parameters**	**learning algorithm**
*.0	AIC=2, BIC=$\log d_i$	none	unsupervised
*.1	β	$\beta \in \mathbb{R}_+$	grid search
*.3	$e^\beta d_i^{w_1} (\max \mathbf{y}_i)^{w_2}$	$\beta, w_1, w_2 \in \mathbb{R}$	interval regression
*.41	$\exp(\beta + \mathbf{w}^\intercal \mathbf{x}_i)$	$\beta \in \mathbb{R}, \mathbf{w} \in \mathbb{R}^{40}$	interval regression

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