

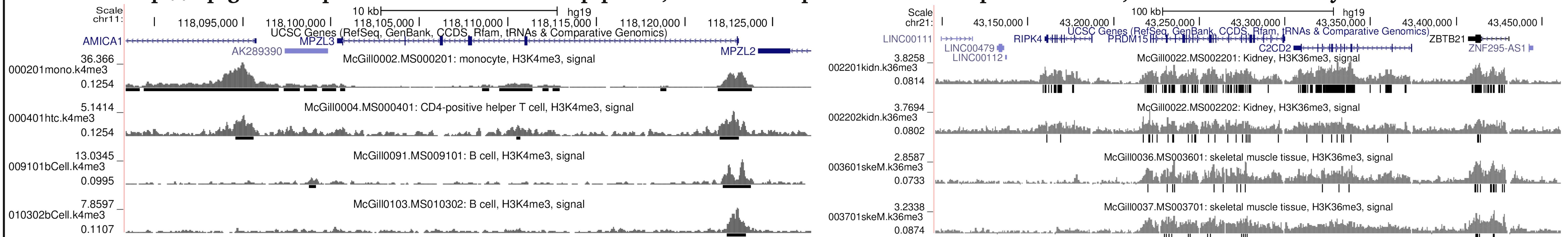
# PeakSeg: Peak detection via constrained optimal Segmentation

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**Introduction:** ChIP-seq data characterize the genomic binding positions for proteins such as histones and transcription factors. The goal of a peak detection algorithm is to filter out background noise, and define the precise genomic positions of "peaks" with many aligned sequence reads.

## Problem: unsupervised peak model does not match visually obvious peaks.

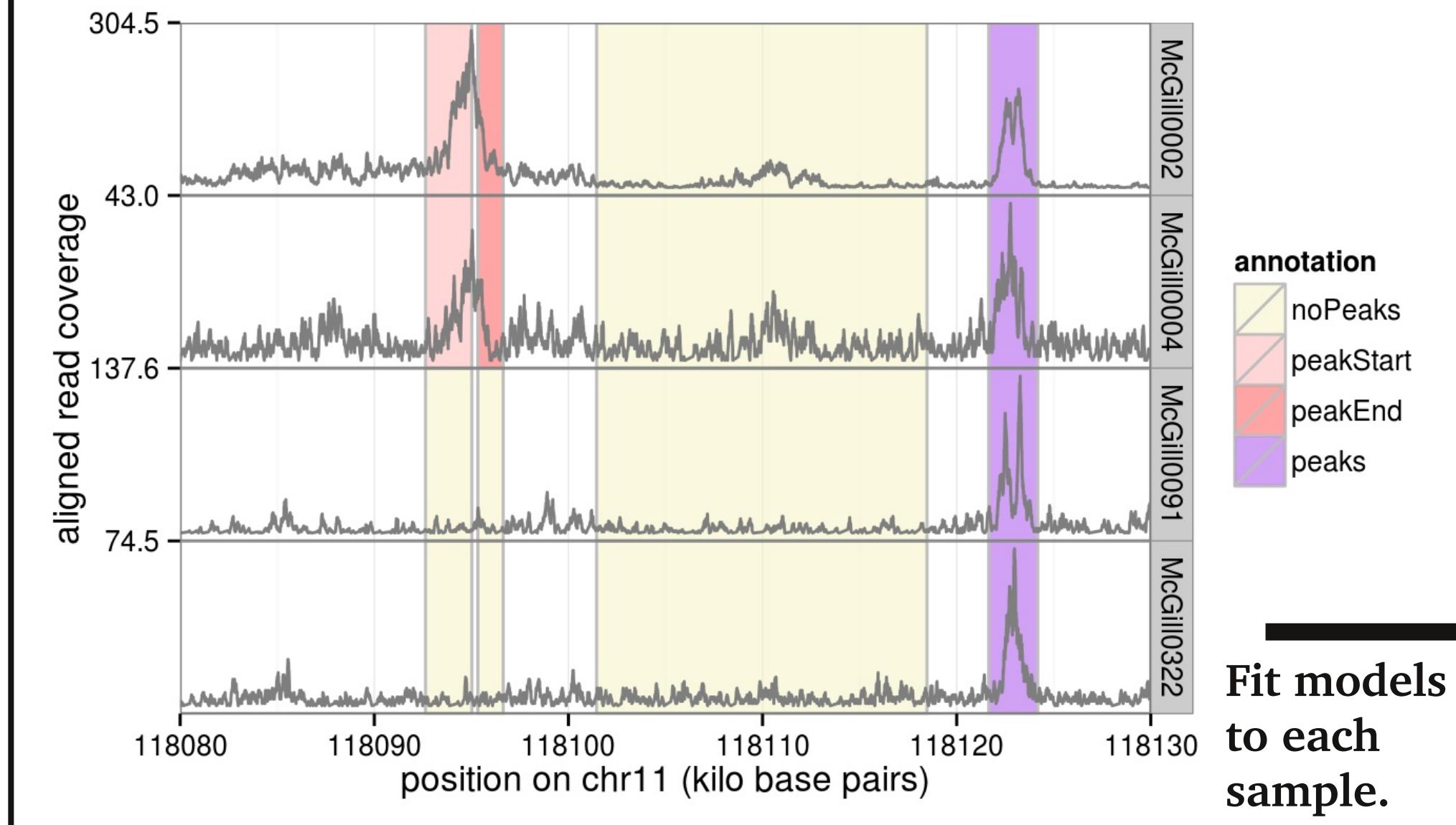
Data from <http://epigenomesportal.ca> H3K4me3 sharp peaks, macs2 unsupervised default peak detector, H3K36me3 broadly enriched domains.



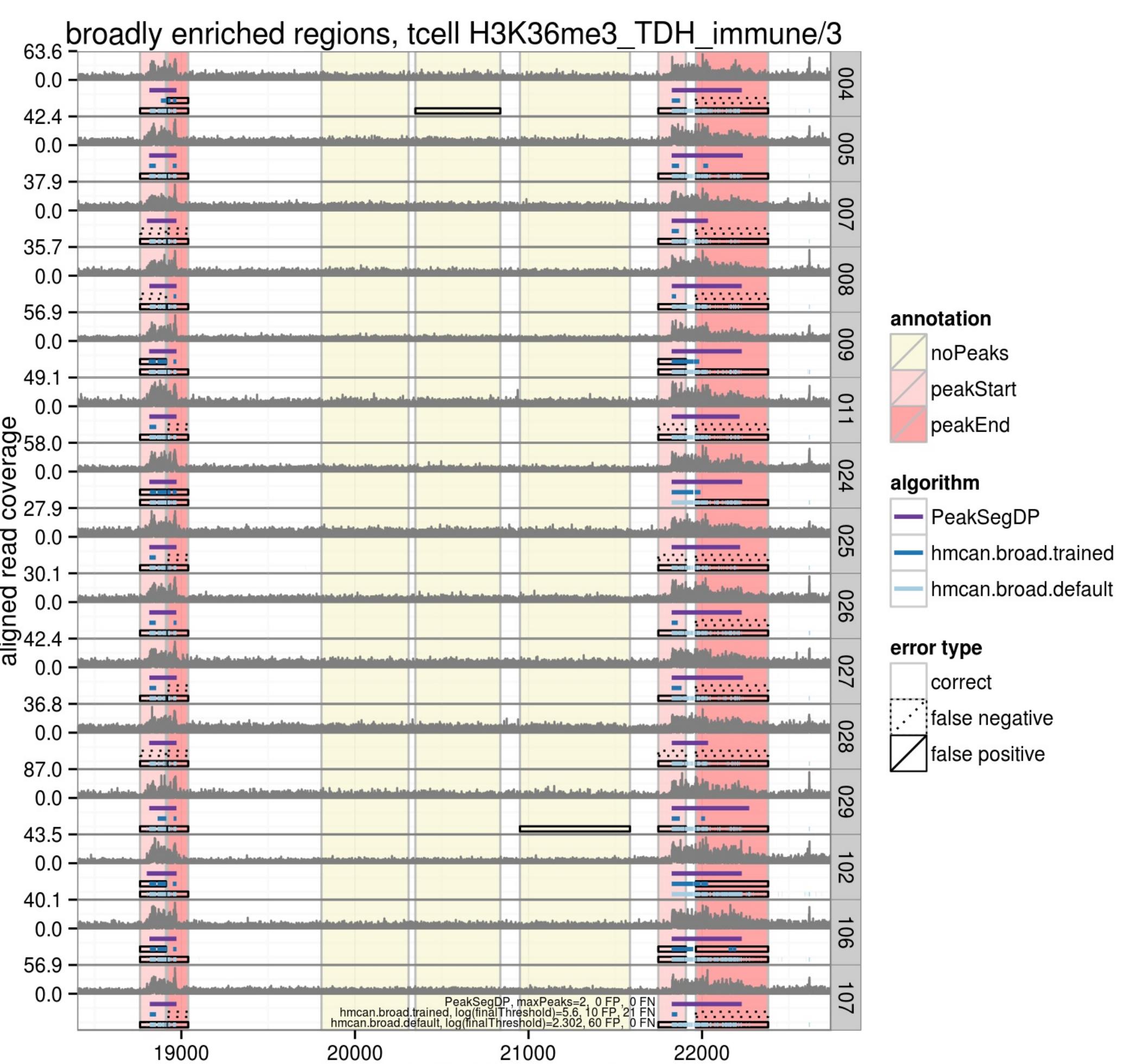
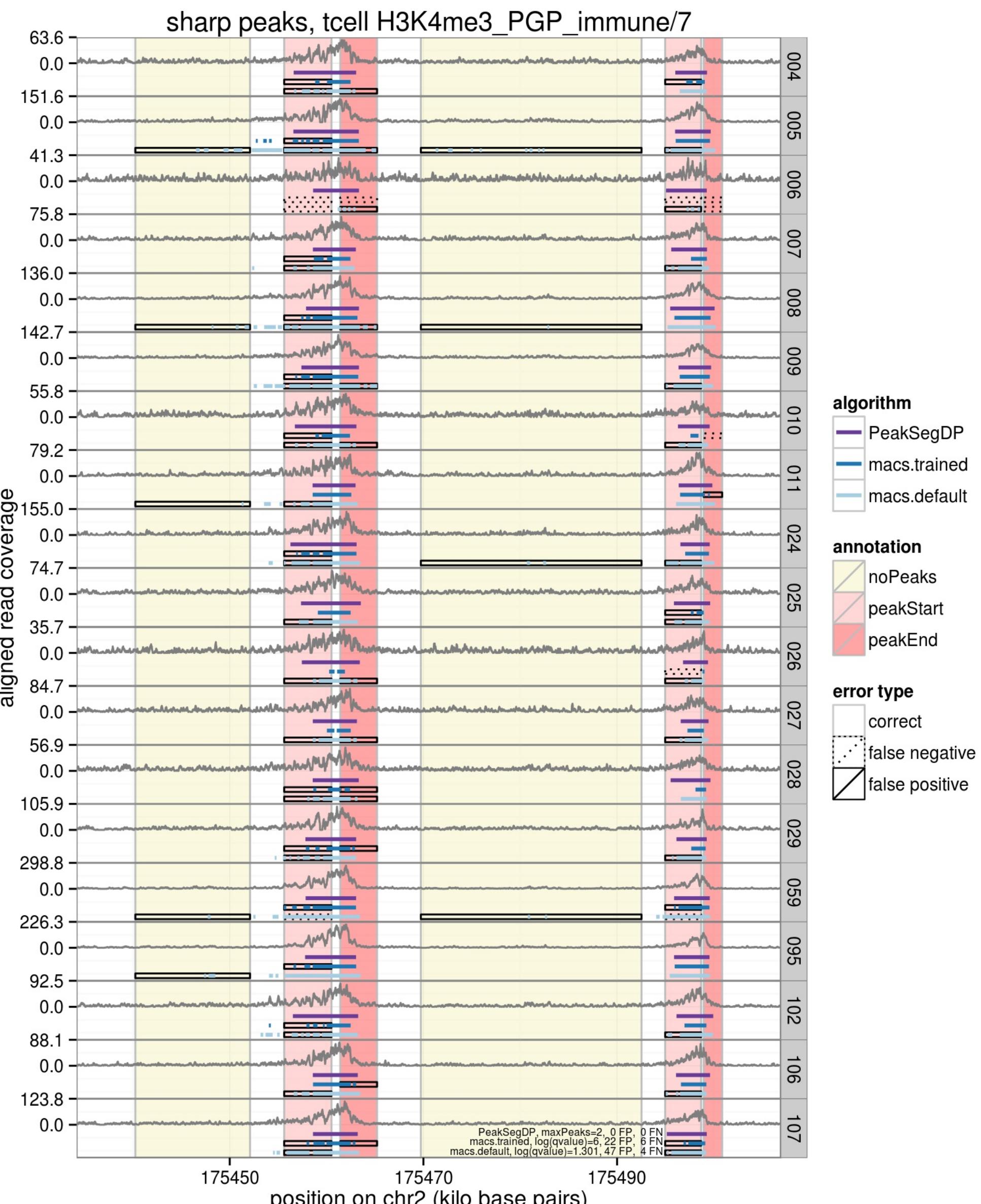
### Benchmark data set: manually annotated regions containing peaks or no peaks.

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

- Seven data sets containing 12,826 manually annotated regions across 37 samples, 8 cell types, from 4 annotators.
- peakStart/peakEnd regions should contain exactly 1 peak start/end.
- peaks regions should contain at least 1 overlapping peak.
- Below: 16 regions across 4 samples created by annotator TDH, 12 possible false positives, 8 possible false negatives.



## Results: State-of-the-art peak detection for both sharp and broad peaks.



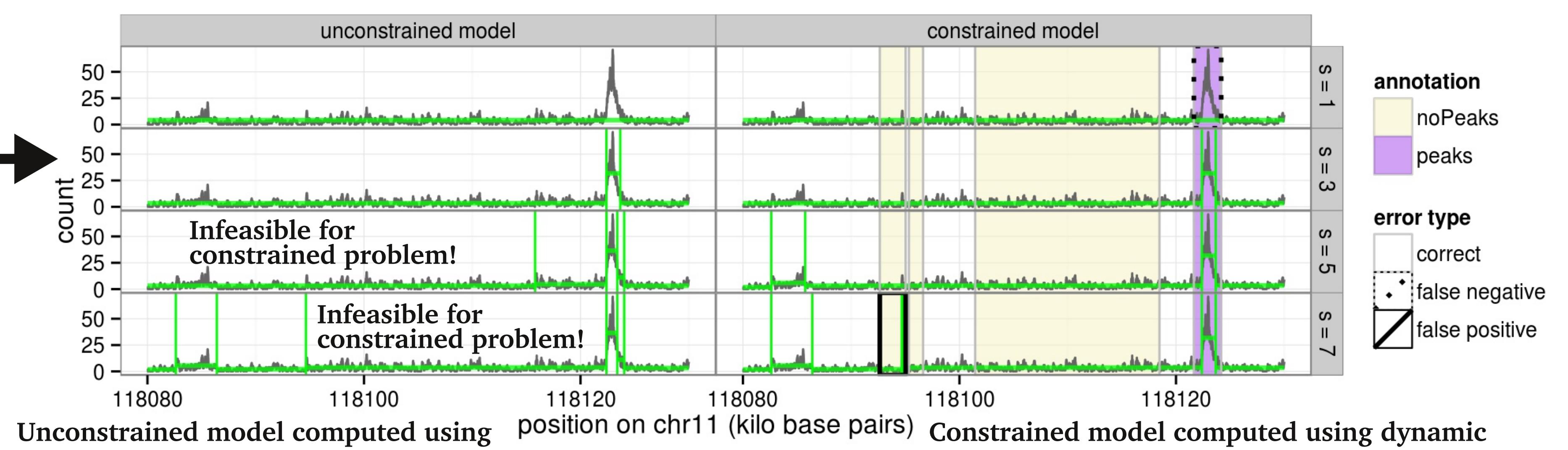
## Proposed Method: constrained maximum likelihood segmentation.

### The Supervised Peak Detection Problem

- A ChIP-seq profile on a single chromosome with  $d$  base pairs is a vector  $\mathbf{y} = [y_1 \dots y_d] \in \mathbb{Z}_+^d$  of counts of aligned sequence reads.
- A peak caller is a function  $c : \mathbb{Z}_+^d \rightarrow \{0, 1\}^d$  which returns 0 for background noise and 1 for a peak.
- We are given  $i \in \{1, \dots, n\}$  profiles  $\mathbf{y}_i$  and annotated regions  $R_i$ .
- The goal is to find a peak caller with minimal error on some test profiles:

$$\text{minimize}_{\mathbf{c}} \sum_{i \in \text{test}} E[c(\mathbf{y}_i), R_i],$$

where  $E$  is the number of false positive and false negative regions  $R_i$ .



Unconstrained model computed using pruned dynamic programming algorithm, Segmentor3IsBack R package, Cleynen et al. Algorithms for Molecular Biology 2014.

Constrained model computed using dynamic programming algorithm, PeakSegDP R package, <https://github.com/tdhock/PeakSegDP>

Errors computed using PeakError R package, <https://github.com/tdhock/PeakError>

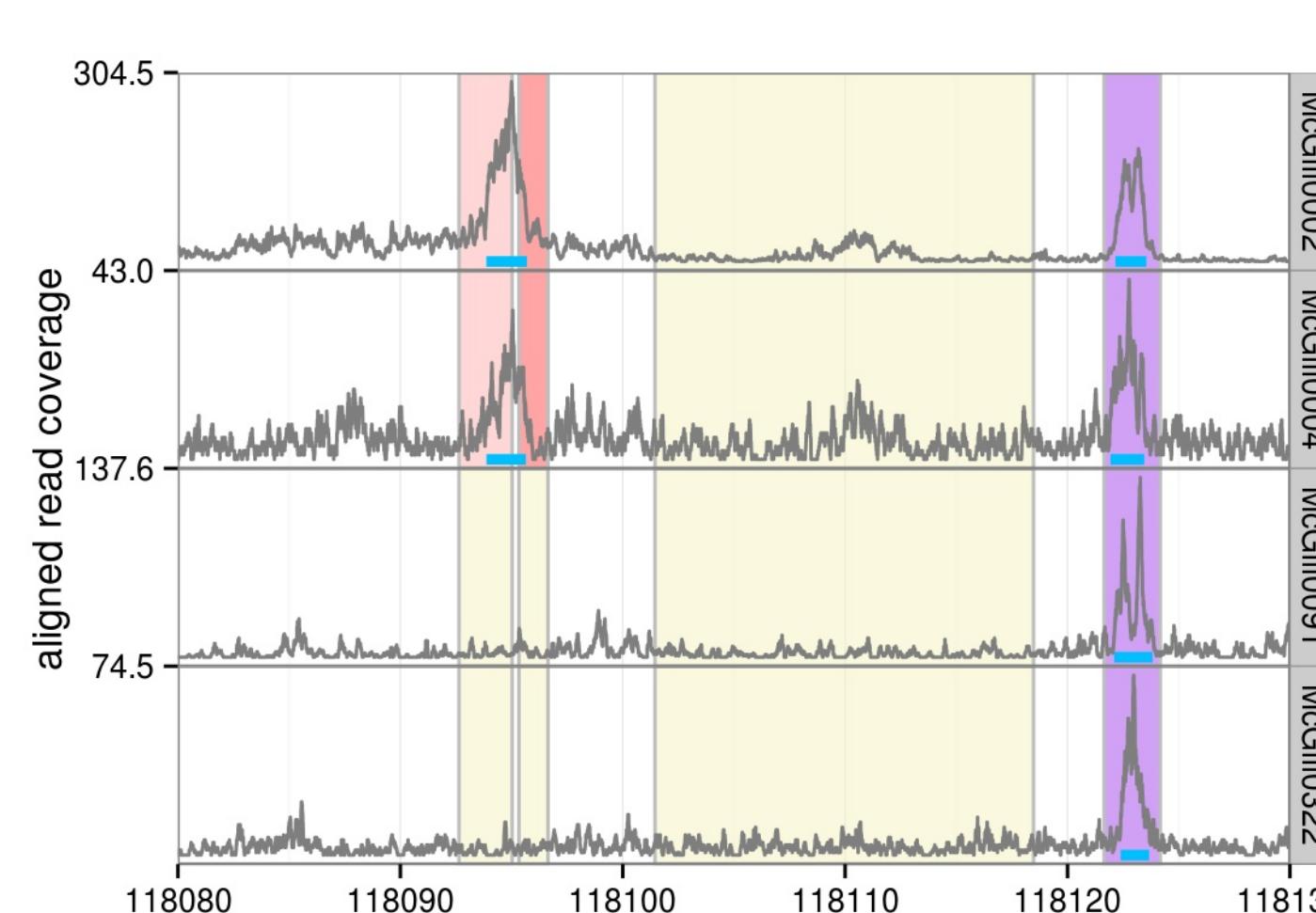
## Supervised PeakSeg: learning a penalty function

Reference: Hocking, Rigaill, et al. Learning Sparse Penalties for Change-point Detection using Max Margin Interval Regression. ICML 2013.

- Given a positive penalty  $\lambda \in \mathbb{R}_+$ , the optimal number of segments is

$$s^*(\lambda, \mathbf{y}) = \arg \min_{s \in \{1, 2, \dots, s_{\max}\}} \rho[\tilde{\mathbf{m}}^s(\mathbf{y}), \mathbf{y}] + \lambda s.$$

- Sample-specific penalty values  $\log \lambda_i = f(\mathbf{x}_i) = \beta + \mathbf{w}^\top \mathbf{x}_i$ .
- An  $m = 2$ -dimensional feature vector  $\mathbf{x}_i = [\log \max \mathbf{y}_i \log d_i]$ , where  $d_i$  is the number of base pairs for sample  $i$ .
- For separable data, find the regression line  $f$  with largest margin:

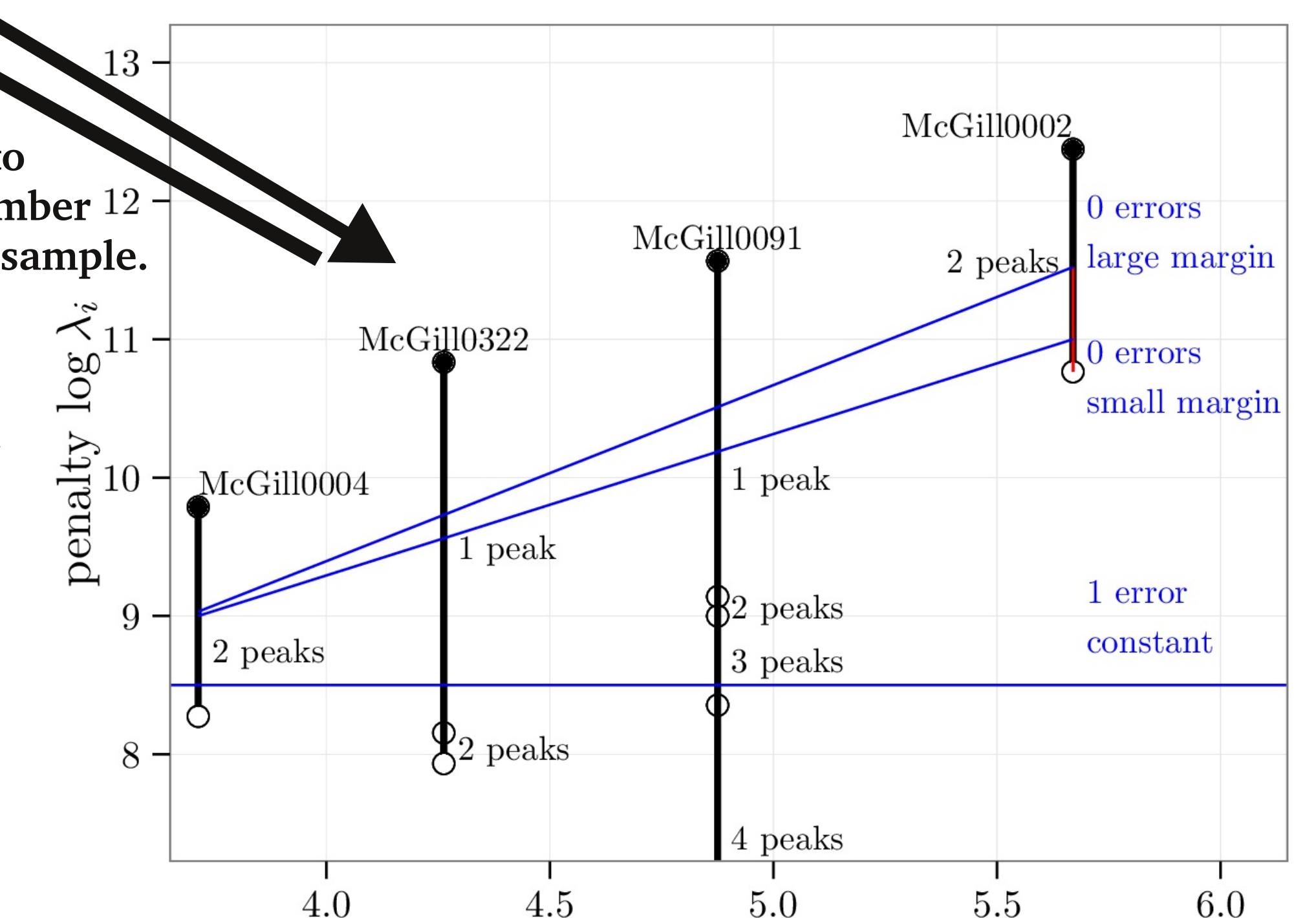


For real data: minimize a smooth convex squared hinge loss  $\ell_i : \mathbb{R} \rightarrow \mathbb{R}_+$  which depends on the annotated region data  $R_i$ :

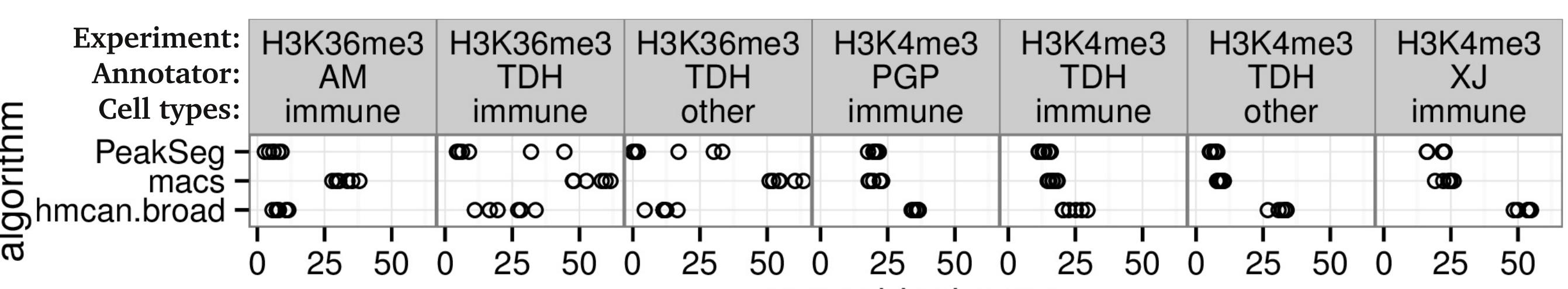
$$\hat{f} = \arg \min_f \sum_{i=1}^n \ell_i[f(\mathbf{x}_i)].$$

To make a prediction on a test sample with profile  $\mathbf{y}$  and features  $\mathbf{x}$ ,

- Compute the predicted penalty  $\hat{\lambda} = \exp \hat{f}(\mathbf{x})$ ,
- the predicted number of segments  $\hat{s} = s^*(\hat{\lambda}, \mathbf{y})$ ,
- and finally the predicted peaks  $\mathbf{P}[\tilde{\mathbf{m}}^{\hat{s}}(\mathbf{y})]$ , where  $\mathbf{P}[\mathbf{m}] = [P_1(\mathbf{m}) \dots P_d(\mathbf{m})] \in \{0, 1\}^d$ .



Experiment: H3K36me3  
Annotator: AM  
Cell types: immune  
PeakSeg: macs  
hmcan.broad: macs



- Consistent results across different annotators.
- When there are few training data (as in H3K36me3 TDH immune/other data sets) PeakSeg suffers from extrapolation, since train features do not overlap test features.

- See extended results (test ROC curves, peak calls) on interactive figure: <http://cbio.ensmp.fr/~thocking/figure-dp-peaks-interactive/>

## Conclusions/future work:

- First supervised peak detector that learns from manually annotated regions with and without peaks.
- State-of-the-art peak detection on both sharp H3K4me3 and broad H3K36me3 profiles.
- Apply to other histone mark types and transcription factor ChIP data.
- Current dynamic programming algorithm has time complexity quadratic in number of data to segment (base pairs), but Pruned Dynamic Programming (Rigaill arXiv:1004.0887) is a linear time algorithm that could be used.
- Other features for penalty learning problem?
- Detecting peaks in the same genomic positions across several samples?