Adaptive sparse Poisson functional regression for the analysis of NGS Data.

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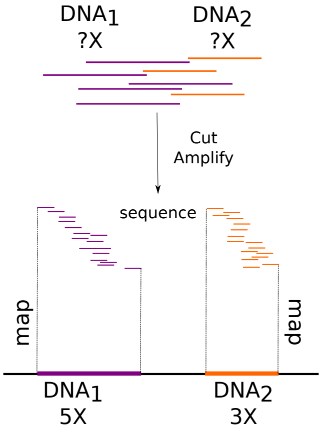
Outline

1. Studying replication by high throughput sequencing
2. Poisson functional regression
3. Calibration of the Lasso weights
4. Simulation study
5. Application on OriSeq data

Next Generation Sequencing Data

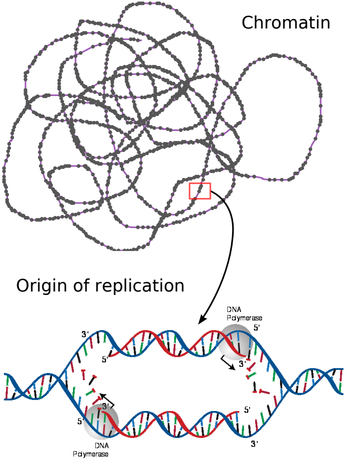
- Massive parallel sequencing of DNA molecules
- Can be used to quantify DNA in a sample
- Expression, copy numbers, DNA-prot. interactions
- Focus on mapped data



Outline of the OriSeq project

- DNA replication: duplication of 1 molecule into 2 daughter molecules
- The exact duplication of mammalian genomes is strongly controlled
- Spatial control (loci choice)
- Temporal control (firing timing)

⇒ What are the (epi)genetic determinants of these controls ?

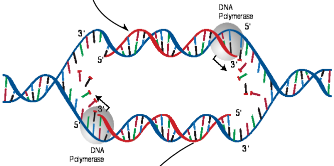


Mapping human replication origins: a technical challenge

- "bubbles" are small and instable (last only minutes by cycle)
- no clear consensus sequence (like in S. Cerevisiae)
- their specification is associated with both DNA sequence and chromatin structure

⇒ *Origin*-Omics: SNS Sequencing

Short Nascent Strand (SNS)



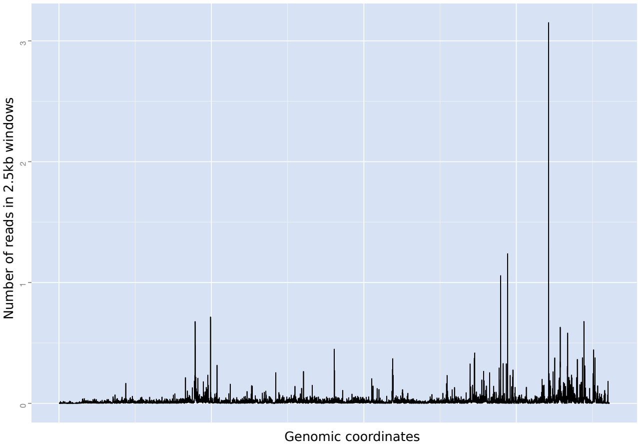
Extraction & Purification

Selection of 1.5-2kb SS fragments

lambda exonuclease Digestion

- qPCR analysis (local)
- DNA tiling arrays
- Sequencing (Ori-Seq)

Example of OriSeq data



Outline

Introduction to Poisson functional Regression

- Y_t the observed number of reads at position X_t on the genome, with $t = 1, \ldots, n$.
- Model sequencing data by functional Poisson regression

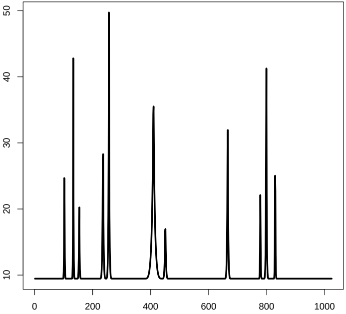
$$Y_t | X_t \sim \mathcal{P}\left(f_0(X_t)\right),$$

- **Goal**: estimate f_0.
- f a candidate estimator of f_0, decomposed on a functional dictionary with p elements $\{\varphi_1, \ldots, \varphi_p\}$:

$$\log f(x) = \sum_{j=1}^{p} \beta_j \varphi_j(x)$$

Dictionaries vs. basis approaches

- The basis approach is designed to catch specific features of the signal ($p = n$)
- If many features are present simultaneously ?
- Consider overcomplete dictionaries ($p > n$)
- Typical dictionaries: Histograms, Daubechies wavelets, Fourier



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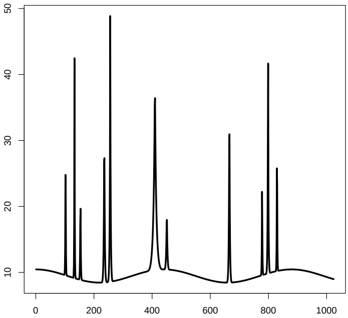

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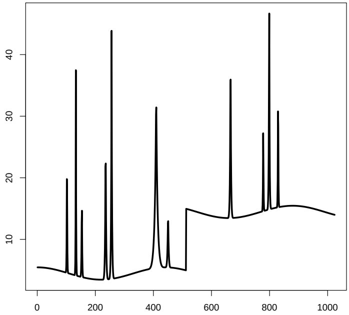

How to select the dictionary elements ?

A Penalized likelihood framework

- We consider a likelihood-based penalized criterion to select $\boldsymbol{\beta}$,
- We denote by $\mathbf{A}$ the $n \times p$-design matrix with $A_{ij} = \varphi_j(X_i)$, $\mathbf{Y} = (Y_1, \ldots, Y_n)^T$
- The log-likelihood of the model is:

$$\log \mathcal{L}(\boldsymbol{\beta}) = \sum_{j \in \mathcal{J}} \beta_j (\mathbf{A}^T \mathbf{Y})_j - \sum_{i=1}^{n} \exp\Big(\sum_{j \in \mathcal{J}} \beta_j A_{ij} \Big) - \sum_{i=1}^{n} \log(Y_i!),$$

- Selection can be performed by the lasso such that:

$$\widehat{\boldsymbol{\beta}} \in \underset{\boldsymbol{\beta} \in \mathbb{R}^p}{\arg\min} \left\{ -\log \mathcal{L}(\boldsymbol{\beta}) + \sum_{j=1}^{p} \lambda_j |\beta_j| \right\}.$$

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Weights calibration using concentration inequalities

- Gaussian framework with noise variance σ^2, weights for the Lasso $\propto \sigma\sqrt{\log p}$
- λ_j is used to control the fluctuations of $\mathbf{A}_j^T \mathbf{Y}$ around its mean,
- key role of V_j, a variance term (the analog of σ^2) defined by

$$V_j = \mathbb{V}(\mathbf{A}_j^T \mathbf{Y}) = \sum_{i=1}^{n} f_0(X_i)\varphi_j^2(X_i).$$

- For any j, we choose a data-driven value for λ_j as small as possible so that with high probability, for any $j \in \{1, ...p\}$,

$$\mathbf{A}_j^T(\mathbf{Y} - \mathbb{E}[\mathbf{Y}])| \leq \lambda_j.$$

Form of the data-driven weights for the Lasso

- Let j be fixed and $\gamma > 0$ be a constant. Define $\widehat{V}_j = \sum_{i=1}^n \varphi_j^2(X_i) Y_i$ the natural unbiased estimator of V_j and

$$\widetilde{V}_j = \widehat{V}_j + \sqrt{2\gamma \log p \widehat{V}_j \max_i \varphi_j^2(X_i)} + 3\gamma \log p \max_i \varphi_j^2(X_i).$$

- Let

$$\lambda_j = \sqrt{2\gamma \log p \widetilde{V}_j} + \frac{\gamma \log p}{3} \max_i |\varphi_j(X_i)|,$$

- then

$$\Pr\left(|\mathbf{A}_j^T(\mathbf{Y} - \mathbb{E}[\mathbf{Y}])| \geq \lambda_j\right) \leq \frac{3}{p^\gamma}.$$

Using the group Lasso for Poisson Functional Regression

- In some situations, coefficients can be grouped:

$$\{1,\ldots,p\} = G_1 \cup \ldots \cup G_K$$

- For wavelets: group by scales for instance (or adjacent positions)
- In this case selection can be performed by the group-Lasso such that:

$$\widehat{\boldsymbol{\beta}} \in \underset{\boldsymbol{\beta}\in\mathbb{R}^p}{\arg\min}\left\{-\log\mathcal{L}(\boldsymbol{\beta}) + \sum_{k=1}^{K}\lambda_k\|\beta_{G_k}\|_2\right\}.$$

- The block ℓ_1-norm on $\mathbb{R}^p$ is defined by:

$$\|\boldsymbol{\beta}\|_{1,2} = \sum_{k=1}^{K}\|\beta_{G_k}\|_2 = \sum_{k=1}^{K}\sqrt{\sum_{j\in G_k}|\beta_j|^2}$$

Form of the data-driven weights for the group-Lasso

- λ_k^g should depend on sharp estimates of the variance parameters $(V_j)_{j \in G_k}$
- Let $k \in \{1, \ldots, K\}$ be fixed and $\gamma > 0$ be a constant. Assume that there exists $M > 0$ such that for any x, $|f_0(x)| \leq M$.
- Let

$$c_k = \sup_{\mathbf{x} \in \mathbb{R}^n} \frac{\|\mathbf{A}_{G_k} \mathbf{A}_{G_k}^T \mathbf{x}\|_2}{\|\mathbf{A}_{G_k}^T \mathbf{x}\|_2}.$$

- For all $j \in G_k$, still with $\widehat{V}_j = \sum_{i=1}^n \varphi_j^2(X_i) Y_i$, define

$$\begin{aligned} \widetilde{V}_j^g &= \widehat{V}_j + \sqrt{2(\gamma \log p + \log |G_k|) \widehat{V}_j \max_i \varphi_j^2(X_i)} \\ &+ 3(\gamma \log p + \log |G_k|) \max_i \varphi_j^2(X_i). \end{aligned}$$

Form of the data-driven weights for the group-Lasso

- Let $\gamma > 0$ be fixed. Define $b_k^i = \sqrt{\sum_{j \in G_k} \varphi_j^2(X_i)}$ and $b_k = \max_i b_k^i$. Finally, we set

$$\lambda_k^g = \left(1 + \frac{1}{2\sqrt{2\gamma \log p}}\right) \sqrt{\sum_{j \in G_k} \widetilde{V}_j^g} + 2\sqrt{\gamma \log p \, D_k},$$

- $D_k = 8Mc_k^2 + 16b_k^2 \gamma \log p$.

$$\Pr\left(\|\mathbf{A}_{G_k}^T(\mathbf{Y} - \mathbb{E}[\mathbf{Y}])\|_2 \geq \lambda_k^g \right) \leq \frac{2}{p^\gamma}.$$

- The form of the weights is analog to the weights in the Gaussian setting
- We show that the associated Lasso / Group Lasso procedure are theoretically optimal (oracle inequalities).
- With a theoretical form for the weights, much computing power is spared !

Outline

Simulation settings

- We considered the classical Donoho & Johnstone functions (Blocks, bumps, doppler, heavisine)
- The intensity function f_0 is set such that (with $\alpha \in \{1, \dots, 7\}$)

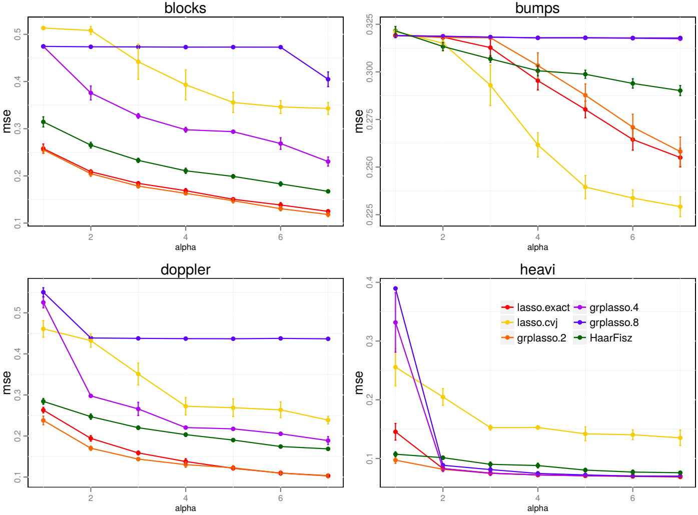
$$f_0 = \alpha \exp g_0$$

- Observations are sampled on a fixed regular grid ($n = 2^{10}$) with $Y_t \sim \mathcal{P}(f_0(X_t))$.
- Use Daubechie, Haar and Fourier as elements of the dictionary
- Check the normalized reconstruction error:

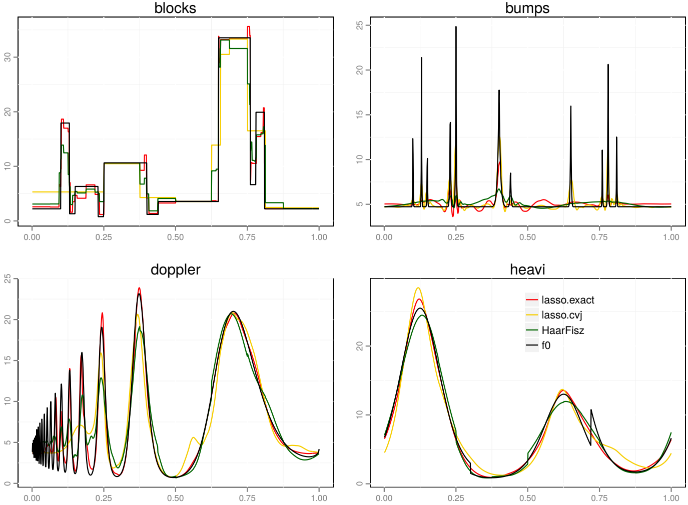
$$MSE = \frac{\|\widehat{f} - f_0\|_2^2}{\|f_0\|_2^2}$$

- Compete with the Haar-Fisz transform and cross-validation

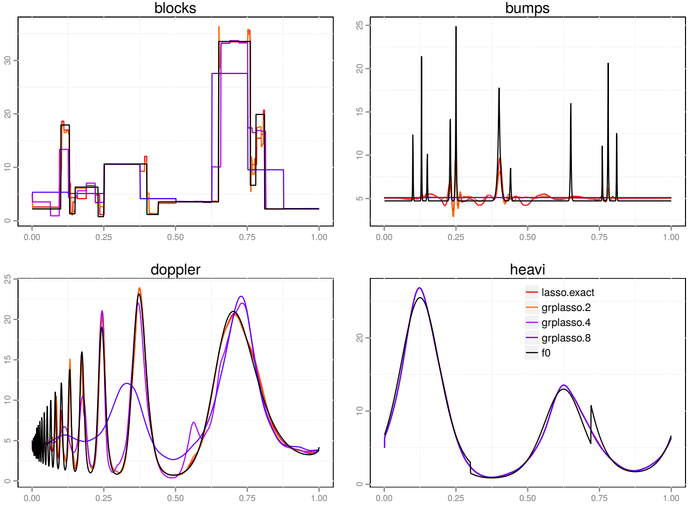
Reconstruction errors



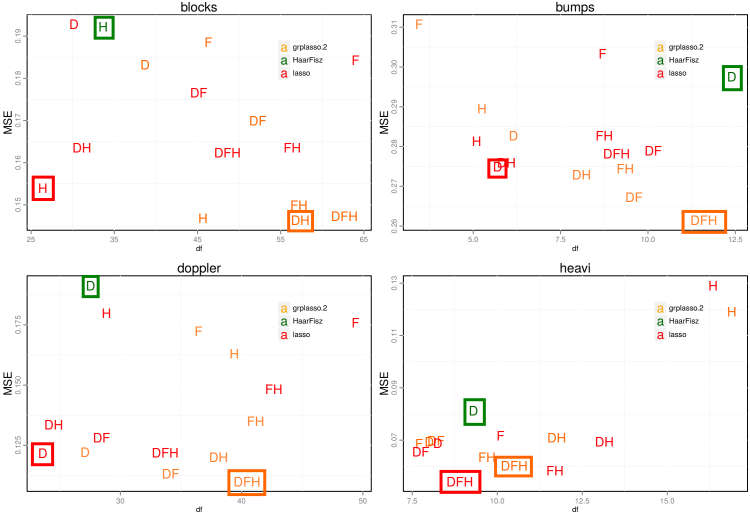
Estimated intensity functions (Lasso)



Estimated intensity functions (group-Lasso)

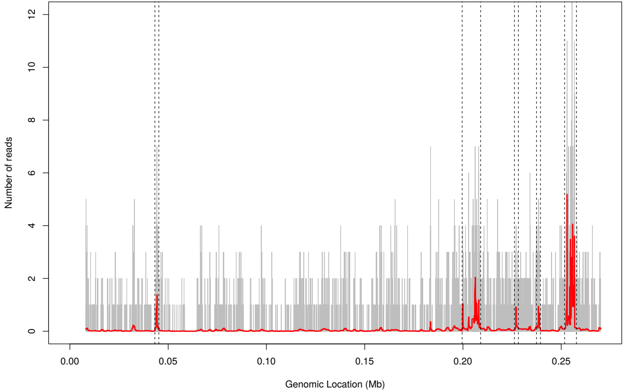


Choosing the best dictionary by cross-validation



Outline

Promising results on OriSeq



Perspective for the integration of multiple datasets

- This model-based framework offers many perspectives for the analysis of peak-like data
- Comparison of two conditions (A vs B) and/or normalization

$$
\begin{aligned}
\log f_A(x) &= \sum_{j \in \mathcal{J}} \beta_j \varphi_j(x) \\
\beta_j &= \alpha_j^{\mathsf{B}} + \gamma_j
\end{aligned}
$$

- Extend to varying coefficients models ($\beta_j(x)$).
- Consider the Negative Binomial distribution
- Preprint: `http://arxiv.org/abs/1412.6966`