Gradient flows for empirical Bayes in high-dimensional linear models

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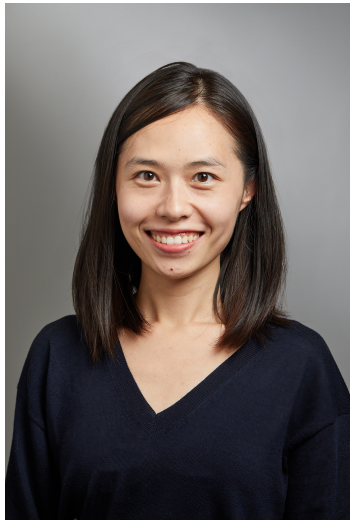
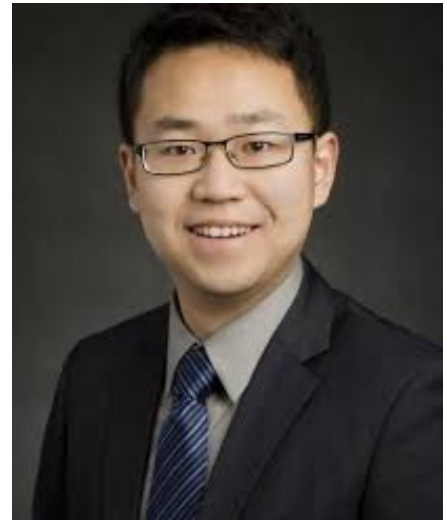
Joint work with



Leying Guan

Yandi Shen



Yihong Wu

Empirical Bayes in the sequence model

Gaussian sequence model

$$\mathbf{y} = \boldsymbol{\theta} + \boldsymbol{\varepsilon} \in \mathbb{R}^p$$

with parameters $\theta_j \overset{iid}{\sim} g_*$, noise $\varepsilon_j \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$.

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Empirical Bayes: Estimate the prior g_* from $\mathbf{y}$, then use the estimated prior for Bayesian inference. [Robbins '50]

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70+ years of literature [Stein '55, Kiefer, Wolfowitz '56, Laird '78, Lindsay '83, Groeneboom, Wellner '92, Ghosal, van der Vaart '01, Zhang '09, ...]

Lindsay 1995, *Mixture models: Theory, geometry, and applications*
Efron 2010, *Large-scale inference*

Empirical Bayes in the linear model

Linear model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\theta} + \boldsymbol{\varepsilon} \in \mathbb{R}^n, \qquad \mathbf{X} \in \mathbb{R}^{n \times p}$$

with random effects $\theta_j \overset{iid}{\sim} g_*$, residual errors $\varepsilon_i \overset{iid}{\sim} \mathcal{N}(0, \sigma^2)$.

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Goal: Estimate the effect size prior g_* from $(\mathbf{X}, \mathbf{y})$ when it is unknown.

1.) When is accurate estimation of g_* statistically possible?
2.) How can we design fast algorithms to perform this estimation?

Motivation from statistical genetics

Bayesian linear models underlie most of the commonly-used methods for genetic analyses of complex (polygenic) traits, where

$\mathbf{y}$ = trait of interest (e.g. human height), $\mathbf{X}$ = genotypes at p variants

- Association testing [EMMAX (Kang et al. '10), BOLT-LMM (Loh et al. '15)]
- Genetic fine-mapping [FINEMAP (Benner et al. '16), SuSiE (Wang et al. '20)]
- Heritability analyses [GCTA (Yang et al. '11)]
- Phenotype prediction [SBayesR (Lloyd-Jones et al. '19), PRS-CS (Ge et al. '19)]

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In these contexts, g_* represents the genetic architecture of the trait.

Many methods for estimating g_* have been developed by the genetics community [Zhang et al. '18, O'Connor '21, Spence et al. '22, Morgante et al. '23].

Correlated vs. "mean-field" designs

For mean-field designs (e.g. $x_{ij} \overset{iid}{\sim} \mathcal{N}(0, \frac{1}{n})$) many approaches can work:

- Direct Gaussian deconvolution of the z-scores $\mathbf{z} = \mathbf{X}^\top \mathbf{y}$

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- Variational inference using mean-field VB [Mukherjee et al. '23] or TAP approximation/AMP [Ahn, Lin, Mei '23], [Celentano, Fan, Lin, Mei '23]

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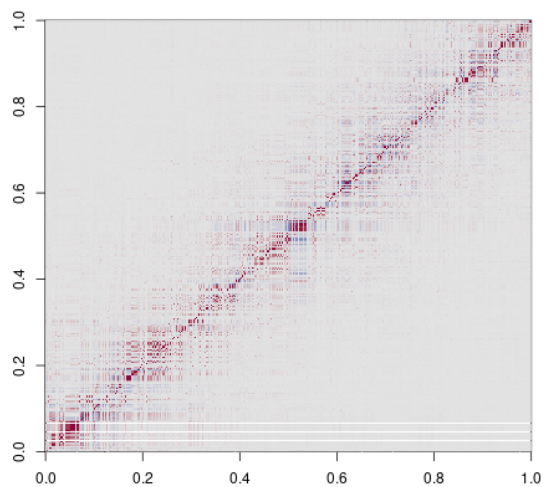
Corresponds to estimating the (marginal) effect size distribution for sparsely sampled genetic variants.



This is different from estimating the conditional/causal effect size distribution in strongly correlated designs.

Outline

Gradient flow computation of the NPMLE

Theoretical results

- Statistical consistency of the NPMLE
- Mixing of Langevin dynamics
- Convergence of the joint gradient flow

Discussion

Outline

Nonparametric maximum likelihood

In the sequence model $\mathbf{y} = \boldsymbol{\theta} + \varepsilon$, the NPMLE $\hat{g}$ is the minimizer of

$$\bar{F}(g) = -\frac{1}{p}\sum_{j=1}^{p} \log[\mathcal{N}_\sigma * g](y_j)$$

where $\mathcal{N}_\sigma \equiv \mathcal{N}(0, \sigma^2)$. [Robbins '50, Kiefer, Wolfowitz '56]

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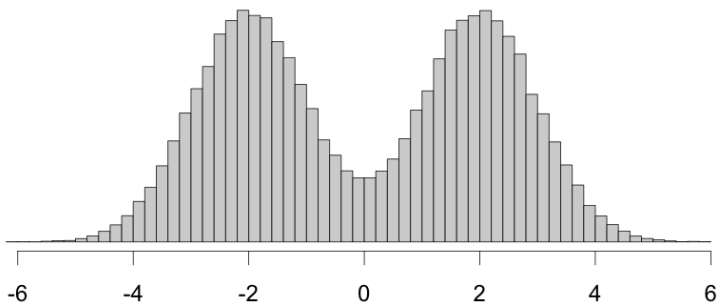
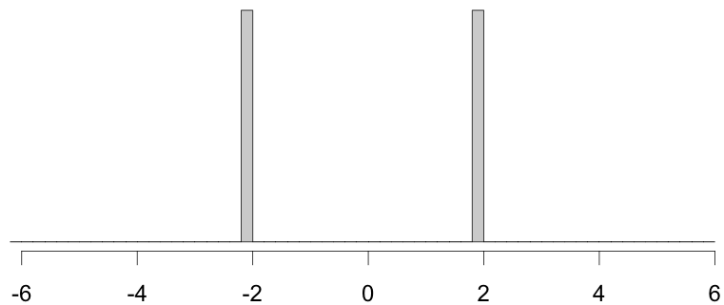


Observed distribution of $\{y_j\}_{j=1}^p$

$\Rightarrow$



Inferred distribution of $\{\theta_j\}_{j=1}^p$

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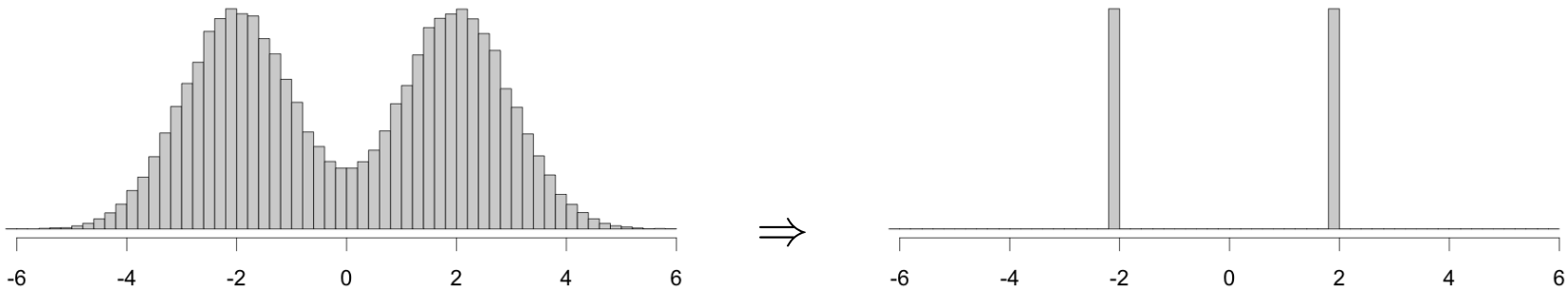

Observed distribution of $\{y_j\}_{j=1}^p$ Inferred distribution of $\{\theta_j\}_{j=1}^p$

The optimization is convex (over probability measures) and efficiently solved by interior point methods [Koenker, Mizera '14]. Gradient flows for optimization were studied by [Yan, Wang, Rigollet '23].

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$$\bar{F}(g) = -\frac{1}{p}\log \int \underbrace{\left(\frac{1}{2\pi\sigma^2}\right)^{n/2} \exp\left(-\frac{1}{2\sigma^2}\|\mathbf{y} - \mathbf{X}\boldsymbol{\theta}\|^2\right)}_{P(\mathbf{y}|\mathbf{X},\boldsymbol{\theta})} \prod_{j=1}^{p} g(\theta_j)\mathrm{d}\theta_j$$

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For general designs $\mathbf{X}$:

- The optimization is non-convex
- The marginal log-likelihood $\bar{F}(g)$ is not coordinate-separable
- Neither $\bar{F}(g)$ nor its gradient is explicitly computable

Existing methods in the linear model

Two common approaches used in practice:

- Monte Carlo Expectation-Maximization (MCEM)
  - **E-step:** Compute $Q(g) = \mathbb{E}_{\boldsymbol{\theta} \sim P(\cdot \mid g^{(t)})}[\log P(\mathbf{y} \mid \mathbf{X}, \boldsymbol{\theta}) + \sum_{j=1}^{p} \log g(\theta_j)]$.
  - **M-step:** Solve $g^{(t+1)} = \arg\max Q(g)$

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  Costly to run MCMC at every E-step, and hard to assess convergence.

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  This approximation is inaccurate when $\mathbf{X}$ has correlated variables.

Reparametrization, variational form, and gradient flow

1. Reparametrize the linear model using smoothed regression coefficients

$$\mathbf{y} = \mathbf{X}\boldsymbol{\varphi} + \tilde{\varepsilon}, \qquad \varphi_1, \ldots, \varphi_p \overset{iid}{\sim} \mathcal{N}_\tau * g_*, \qquad \tilde{\varepsilon} \sim \mathcal{N}(0, \sigma^2 \mathbf{I} - \tau^2 \mathbf{X}\mathbf{X}^\top)$$

   Inspired by a proof of LSI in [Bauerschmidt, Bodineau '18].

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2. Write the Gibbs variational representation

$$\bar{F}(g) = \min_{q \in \mathcal{P}(\mathbb{R}^p)} F(q, g) \text{ where}$$

$$F(q,g) = -\frac{1}{p} \int \Bigg[\underbrace{\log P(\mathbf{y} \mid \mathbf{X}, \boldsymbol{\varphi}) + \sum_{j=1}^{p} \log[\mathcal{N}_\tau * g](\varphi_j)}_{:= U_g(\boldsymbol{\varphi})} - \log q(\boldsymbol{\varphi}) \Bigg] \mathrm{d}q(\boldsymbol{\varphi})$$

   Here, g is the (1-dimensional) entrywise prior for $\boldsymbol{\theta}$, and q is the (p-dimensional) posterior for $\boldsymbol{\varphi} = \boldsymbol{\theta} + \mathcal{N}(0, \tau^2\mathbf{I})$.

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3. Optimize $F(q, g)$ jointly over (q, g) via the gradient flows

$$\partial_t q_t = -p \cdot \operatorname{grad}_q^{W_2} F(q_t, g_t), \qquad \partial_t g_t = -\operatorname{grad}_g^{\mathrm{FR}} F(q_t, g_t)$$

Wasserstein-2 gradient flow in q

The gradient flow equation in the posterior $q(\varphi)$ is

$$\begin{aligned}\partial_t q_t(\varphi) &= -p \cdot \operatorname{grad}_q^{W_2} F(q_t, g_t) \\ &= -\nabla \cdot \Big[q_t(\varphi) \nabla U_{g_t}(\varphi) \Big] + \Delta q_t(\varphi)\end{aligned}$$

This is the Fokker-Planck equation for the density evolution under a Langevin diffusion

$$\mathrm{d}\varphi_t = \nabla U_{g_t}(\varphi)\,\mathrm{d}t + \sqrt{2}\,\mathrm{d}\mathbf{B}_t$$

with time-evolving drift. [Jordan, Kinderlehrer, Otto '98]

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In our implementations we use a forward Euler discretization in time, leading to an Unadjusted Langevin Algorithm [Roberts, Tweedie '96].

Fisher-Rao gradient flow in g

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$$\partial_t g_t(\theta) = -\operatorname{grad}_g^{\mathrm{FR}} F(q_t, g_t) = g_t(\theta)\Big(\Big[\mathcal{N}_\tau * \frac{\bar{q}_t}{\mathcal{N}_\tau * g_t}\Big](\theta) - 1\Big)$$

where $\bar{q}_t$ is the average marginal distribution of $\varphi_1, \ldots, \varphi_p$ under q_t.

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We estimate $\bar{q}_t$ using the empirical distribution of coordinates of the current Langevin iterate, $\bar{q}_t \approx \frac{1}{p}\sum_{j=1}^p \delta_{\varphi_{t,j}}$,

$$\Big[\mathcal{N}_\tau * \frac{\bar{q}_t}{\mathcal{N}_\tau * g_t}\Big](\theta) \approx \frac{1}{p}\sum_{j=1}^p \frac{\mathcal{N}_\tau(\theta - \varphi_{t,j})}{\mathcal{N}_\tau * g_t(\varphi_{t,j})}$$

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For fixed $\boldsymbol{\varphi} \equiv \boldsymbol{\varphi}_t$, the resulting gradient flow has the simple interpretation of a Fisher-Rao flow on the log-likelihood of the sequence model

$$\boldsymbol{\varphi} = \boldsymbol{\theta} + \mathcal{N}(0, \tau^2 \mathbf{I}), \qquad \theta_1, \ldots, \theta_p \overset{iid}{\sim} g_*$$

EBflow

To summarize, EBflow is a time-discretization of

$$\mathrm{d}\boldsymbol{\varphi}_t = \nabla U_{g_t}(\boldsymbol{\varphi}_t)\,\mathrm{d}t + \sqrt{2}\,\mathrm{d}\mathbf{B}_t \tag{1}$$

$$\partial_t g_t(\theta) = g_t(\theta) \cdot \left(\frac{1}{p} \sum_{j=1}^{p} \frac{\mathcal{N}_\tau(\theta - \varphi_{t,j})}{\mathcal{N}_\tau * g_t(\varphi_{t,j})} - 1 \right) \tag{2}$$

where

- $\boldsymbol{\varphi}_t$ follows the Langevin diffusion (1) for the posterior law of $\boldsymbol{\varphi} = \boldsymbol{\theta} + \mathcal{N}(0, \tau^2)$ with time-evolving prior $\mathcal{N}_\tau * g_t$.
- g_t follows (2) which is a gradient flow for computing the NPMLE from the coordinates of $\boldsymbol{\varphi}_t$.

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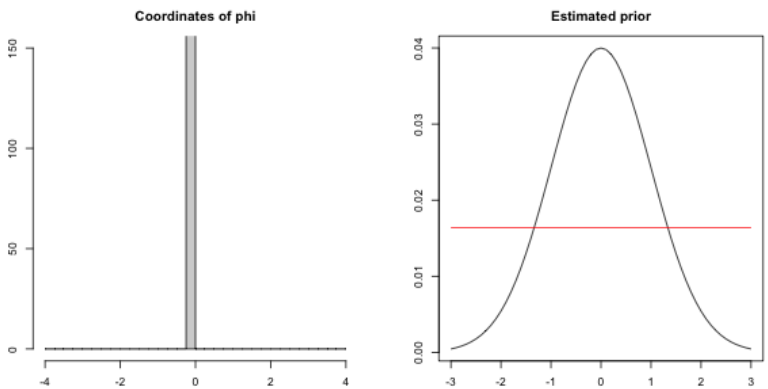
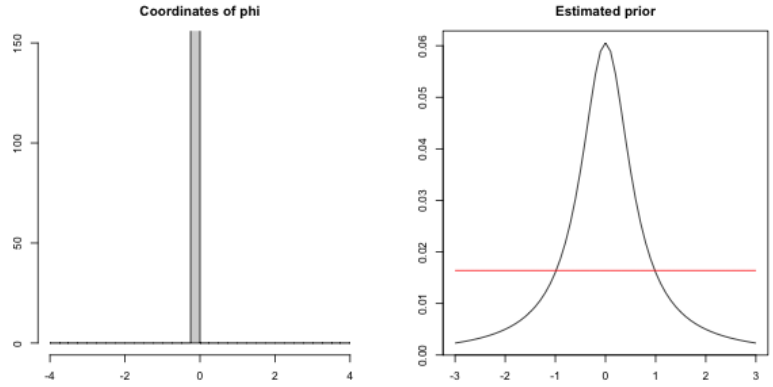
A similar idea of jointly optimizing the Gibbs variational objective was proposed in [Kuntz, Lim, Johansen '23] for general latent variable models, focusing on "low-dimensional" problems with parametric priors.

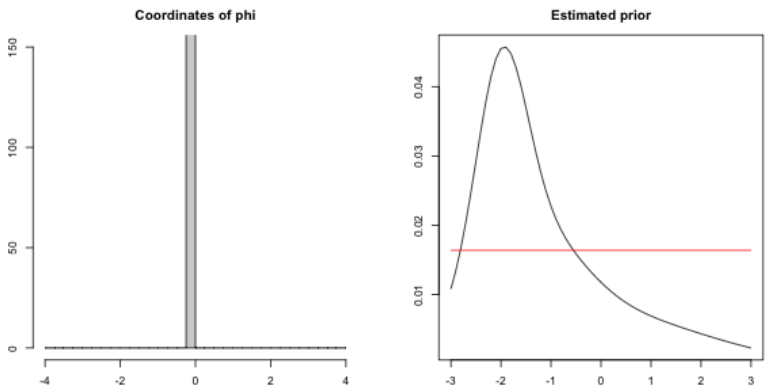
Illustrations for various priors



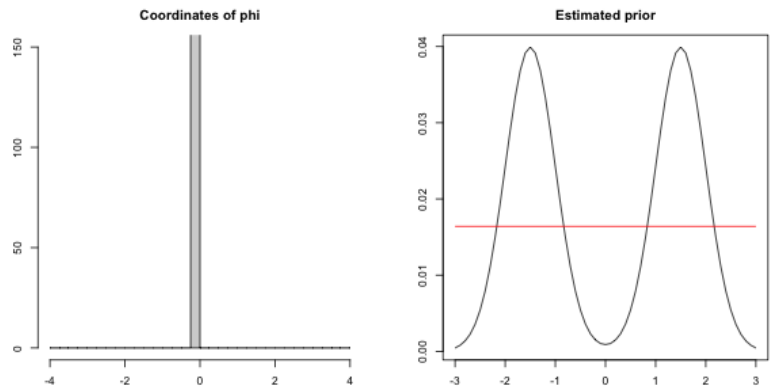
Gaussian



Cauchy



Skew



Bimodal

$n = 1000$, $p = 500$ variables in pairs w/ 90%-correlation.

EBflow was performed with a small spline smoothing regularizer, pre-conditioning of the Langevin diffusion, and log-linear step size decay.

Relation to mean-field VI and EM

Empirical Bayes within mean-field VI [Bernardo et al. '03] solves

$$(\hat{q}, \hat{g}) = \underset{q \in \mathcal{Q},\, g \in \mathcal{P}(\mathbb{R})}{\arg\min} \; F(q, g), \quad \mathcal{Q} = \{\text{product measures on } \mathbb{R}^p\}$$

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EM performs coordinate descent [Neal, Hinton '98]

$$q^{(t)} = \underset{q \in \mathcal{P}(\mathbb{R}^p)}{\arg\min}\, F(q, g^{(t)}), \qquad g^{(t+1)} = \underset{g \in \mathcal{P}(\mathbb{R})}{\arg\min}\, F(q^{(t)}, g)$$

Relation to mean-field VI and EM

Empirical Bayes within mean-field VI [Bernardo et al. '03] solves

$$(\hat{q}, \hat{g}) = \underset{q \in \mathcal{Q},\, g \in \mathcal{P}(\mathbb{R})}{\arg\min} \; F(q, g), \quad \mathcal{Q} = \{\text{product measures on } \mathbb{R}^p\}$$

EM performs coordinate descent [Neal, Hinton '98]

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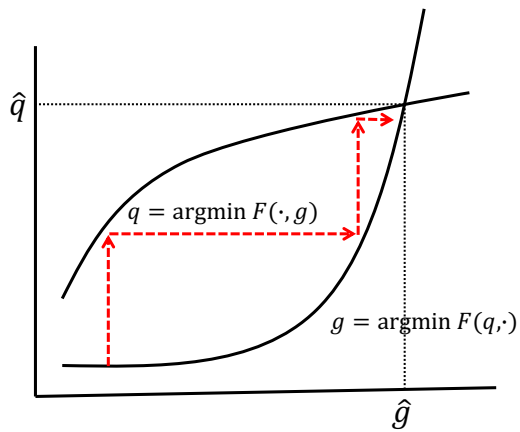

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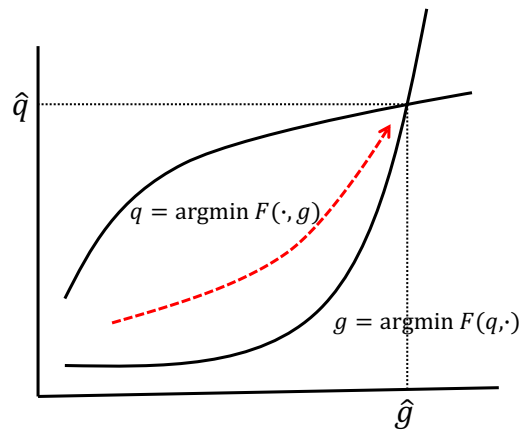
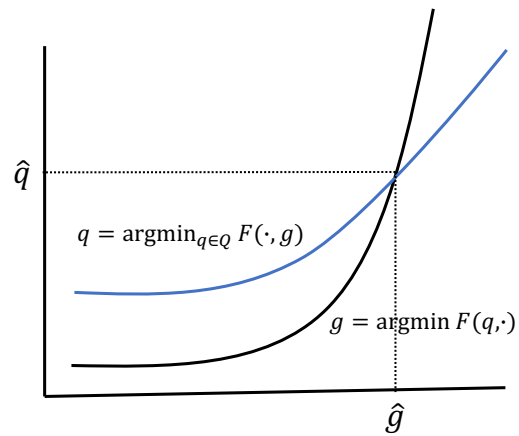


EBflow



VI

Outline

Outline

NPMLE consistency when $n \geq p$

Linear model

$$\mathbf{y} = \mathbf{X}\boldsymbol{\theta} + \boldsymbol{\varepsilon} \in \mathbb{R}^n, \qquad \mathbf{X} \in \mathbb{R}^{n \times p}, \qquad \theta_1, \ldots, \theta_p \overset{iid}{\sim} g_*$$

When is accurate estimation of g_* statistically possible?

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When is accurate estimation of g_* statistically possible?

If $n \geq p$ and $\mathbf{X}$ has full column rank, the model is equivalent to observing

$$\hat{\boldsymbol{\theta}}_{\mathrm{OLS}} = (\mathbf{X}^\top \mathbf{X})^{-1} \mathbf{X}^\top \mathbf{y} = \boldsymbol{\theta} + \underbrace{(\mathbf{X}^\top \mathbf{X})^{-1} \mathbf{X}^\top \boldsymbol{\varepsilon}}_{\text{colored Gaussian noise}}$$

Theorem (Mukherjee, Sen, Sen '23)

Suppose $g_* \in \mathcal{P}([-M, M])$, and $\bar{F}(\hat{g}) \leq \bar{F}(g_*) + o_{\mathbb{P}}(1)$. As $n, p \to \infty$, if $\mathbf{X}$ has full column rank and $\lambda_{\min}(\mathbf{X}^\top \mathbf{X}) \asymp \lambda_{\max}(\mathbf{X}^\top \mathbf{X}) \asymp 1$, then

$$\hat{g} \xrightarrow{\mathbb{P}} g_* \text{ weakly.}$$

NPMLE consistency when $n < p$

If $n < p$, then $\mathbf{y}$ depends on $\boldsymbol{\theta}$ only via its projection onto $\operatorname{row\,span}(\mathbf{X})$.

When is g_* (stably) recoverable from the projection of $g_*^{\otimes p}$ onto a subspace of $\mathbb{R}^p$ of dimension $n < p$?

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Assumption

Suppose $n, p \to \infty$ with $\lambda_{\max}(\mathbf{X}^\top \mathbf{X}) \lesssim 1$, $\|\mathbf{X}\frac{\mathbf{1}}{\sqrt{p}}\|_2^2 \gtrsim 1$, and for a subset of variables $\mathcal{S}$ of cardinality $|\mathcal{S}| \asymp p$ and each $j \in \mathcal{S}$, there exists a test vector $\mathbf{z}_j \in \mathbb{R}^n$ such that

$$\langle \mathbf{z}_j, \mathbf{x}_j \rangle \to 1, \qquad \sum_{k \neq j} |\langle \mathbf{z}_j, \mathbf{x}_k \rangle|^{2+\varepsilon} \to 0.$$

[Intuition: Then by the CLT, $\mathbf{z}_j^\top \mathbf{y} \approx \theta_j +$ Gaussian noise.]

Condition is reminiscent of the debiased lasso in [Zhang, Zhang '14]. However, here $\mathbf{z}_j$ does *not* need to be estimable from the data $(\mathbf{X}, \mathbf{y})$.

NPMLE consistency when $n < p$

Theorem (F., Guan, Shen, Wu)

Suppose $g_* \in \mathcal{P}([-M, M])$, and $\bar{F}(\hat{g}) \le \bar{F}(g_*) + o_{\mathbb{P}}(1)$. Under the preceding assumption, as $n, p \to \infty$,

$$\hat{g} \xrightarrow{\mathbb{P}} g_* \text{ weakly.}$$

Example (random design)

Suppose $n, p \to \infty$ with

- $n/p \ge \gamma$ any positive constant
- $\mathbf{X}$ has i.i.d. subgaussian rows $\{\frac{1}{\sqrt{n}} x^{(i)}\}$ where $\mathbb{E} x^{(i)} = 0$, $\operatorname{Cov} x^{(i)} = \mathbf{\Sigma}$,

$$\lambda_{\min}(\mathbf{\Sigma}) \asymp \lambda_{\max}(\mathbf{\Sigma}) \asymp 1.$$

Then the assumptions hold, for z_j depending on Σ (typically unknown).

Outline

High-temperature log-Sobolev inequality

When does the gradient flow of q_t for an arbitrary *fixed* prior g converge in polynomial time to the posterior law

$$P_g(\boldsymbol{\varphi} \mid \mathbf{X}, \mathbf{y}) \propto P(\mathbf{y} \mid \mathbf{X}, \boldsymbol{\varphi}) \prod_{j=1}^{p} [\mathcal{N}_\tau * g](\varphi_j)?$$

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Let $g \in \mathcal{P}([-M, M])$ and suppose $\sigma^2 > M^2 \|\mathbf{X}\|^2$. Then $P_g(\varphi \mid \mathbf{X}, \mathbf{y})$ satisfies the LSI, for a constant $C = C(M, \tau) > 0$ (uniform over g)

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- Implies exponential contraction of $D_{\mathrm{KL}}(q_t(\varphi) \| P_g(\varphi \mid \mathbf{X}, \mathbf{y}))$ when the prior g is fixed (and possibly misspecified).
- LSI holds also for the posterior $P(\boldsymbol{\theta} \mid \mathbf{X}, \mathbf{y})$ in the $\boldsymbol{\theta}$ parameter when $g(\cdot)$ has density bounded away from $\{0, \infty\}$.

High-temperature log-Sobolev inequality

Consider the generative process

$$\theta_j \overset{iid}{\sim} g \Rightarrow \varphi'_j = \theta_j + \mathcal{N}(0, \tau'^2) \Rightarrow \mathbf{y} \sim \mathcal{N}(\mathbf{X}\boldsymbol{\varphi}', \sigma^2\mathbf{I} - \tau'^2\mathbf{X}\mathbf{X}^\top)$$

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This gives a mixture-of-products representation (analogous to [Bauerschmidt, Bodineau '18] for high-temperature spin systems)

$$P_g(\boldsymbol{\theta} \mid \mathbf{X}, \mathbf{y}) = \int P_g(\boldsymbol{\theta} \mid \boldsymbol{\varphi}') P_g(\boldsymbol{\varphi}' \mid \mathbf{X}, \mathbf{y}) \, \mathrm{d}\boldsymbol{\varphi}'$$

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- For $\tau'^2 > M^2$, the prior $\mathcal{N}_{\tau'} * g$ is strongly log-concave for any $g \in \mathcal{P}([-M, M])$, hence so is $P_g(\boldsymbol{\varphi}' \mid \mathbf{X}, \mathbf{y})$. LSI holds by Bakry-Emery.

This implies LSI for $P_g(\boldsymbol{\theta} \mid \mathbf{X}, \mathbf{y})$.

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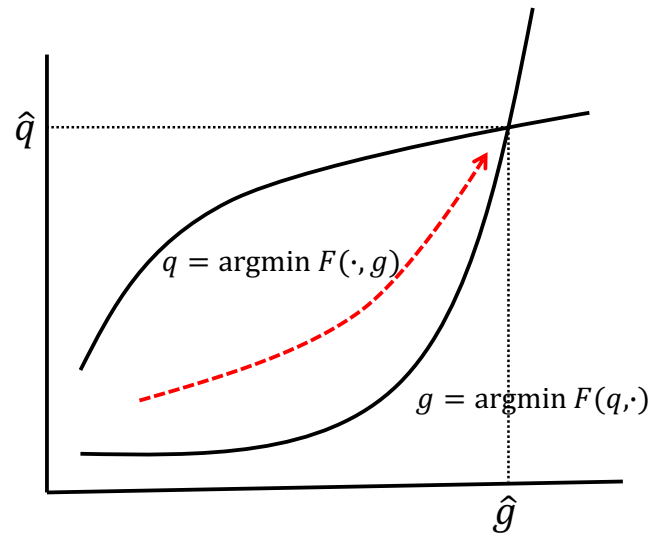
LSI for $P_g(\boldsymbol{\varphi} \mid \mathbf{X}, \mathbf{y})$ is similar, without needing bounds on $g(\cdot)$.

Outline

Convergence of the joint flow

When does g_t under the joint gradient flow of $\{q_t, g_t\}$ converge (in polynomial time) to an approximate NPMLE?



LSI implies contraction of $D_{\mathrm{KL}}(q_t(\varphi) \| P_{g_t}(\varphi \mid \mathbf{X}, \mathbf{y}))$, not of $D_{\mathrm{KL}}(q_t(\varphi) \| P_{g_*}(\varphi \mid \mathbf{X}, \mathbf{y}))$.

In general $F(q, g)$ may have multiple local minimizers, in 1-to-1 correspondence with local minimizers of $\bar{F}(g)$.

Convergence of the joint flow

Theorem (F., Guan, Shen, Wu)

Suppose $P_g(\varphi \mid \mathbf{X}, \mathbf{y})$ *satisfies a LSI uniformly over* $g \in \mathcal{P}([-M, M])$, *and* $\bar{F}$ *is convex over the sub-level set* $\{g : \bar{F}(g) \leq F(q_0, g_0)\}$.

Then under mild conditions for the initialization (q_0, g_0), *for any* $\varepsilon > 0$ *and some* $t \lesssim \varepsilon^{-2+o(1)}(n+p)$,

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- Local convexity is required for $\bar{F}(g)$, not for $F(q, g)$.
- In asymptotic settings where $\bar{F}(g)$ converges to a deterministic limit, it is convex on a sub-level set that is dimension-free.

Roles of variable reparametrization

Parametrization of the model as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\varphi} + \tilde{\varepsilon}, \qquad \boldsymbol{\varphi} = \boldsymbol{\theta} + \mathcal{N}(0, \tau^2 \mathbf{I})$$

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- Ensuring uniform smoothness of the Langevin diffusion drift, for existence, uniqueness, and smoothness of the solution $\{q_t, g_t\}$.

Outline

Summary

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$$\partial_t g_t = -\operatorname{grad}_g^{\mathrm{FR}} F(q_t, g_t)$$
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- The prior g_t is 1-dimensional, and the form of $\partial_t g_t$ depends only on $\bar{q}_t$ which is easier to estimate than q_t.

Future directions / Open questions

- Can one analyze the optimization landscape of $\bar{F}(g)$, perhaps in restricted settings (e.g. high noise or i.i.d. Gaussian designs)?

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- Extensions to other high-dimensional regression models (e.g. GLMs) and other Monte Carlo sampling procedures?

Reference

Z. Fan, L. Guan, Y. Shen, Y. Wu. "Gradient flows for empirical Bayes in high-dimensional linear models," https://arxiv.org/abs/2312.12708