# Machine Learning and Statistics in Genetics and Genomics 

IV: Regularized and Bayesian regression

## Christoph Lippert

Microsoft Research<br>eScience group

Research
Los Angeles, USA

Current topics in computational biology UCLA
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## Linear Regression II

Bayesian linear regression

Model comparison and hypothesis testing

Summary

Outline

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## Regression

Linear regression:

- Making predictions
- Comparison of alternative models
Bayesian and regularized regression:



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- Uncertainty in model parameters



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Linear regression:

- Making predictions
- Comparison of alternative models
Bayesian and regularized regression:
- Uncertainty in model parameters
- Generalized basis functions



## Further reading, useful material

- Christopher M. Bishop: Pattern Recognition and Machine learning
- Sam Roweis: Gaussian identities

Outline

## Regression

## Noise model and likelihood

- Given a dataset $\mathcal{D}=\left\{\boldsymbol{x}_{n}, y_{n}\right\}_{n=1}^{N}$, where $\boldsymbol{x}_{n}=\left\{x_{n, 1}, \ldots, x_{n, D}\right\}$ is $D$ dimensional (for example $D$ SNPs), fit parameters $\boldsymbol{\theta}$ of a regressor $f$ with added Gaussian noise:

$$
y_{n}=f\left(\boldsymbol{x}_{n} ; \boldsymbol{\theta}\right)+\epsilon_{n} \quad \text { where } \quad p\left(\epsilon \mid \sigma^{2}\right)=\mathcal{N}\left(\epsilon \mid 0, \sigma^{2}\right) .
$$

- Equivalent likelihood formulation:

$$
p(\boldsymbol{y} \mid \boldsymbol{X})=\prod_{n=1}^{N} \mathcal{N}\left(y_{n} \mid f\left(\boldsymbol{x}_{n} ; \boldsymbol{\theta}\right), \sigma^{2}\right)
$$

## Regression

Choosing a regressor

- Choose $f$ to be linear:

$$
p(\boldsymbol{y} \mid \boldsymbol{X})=\prod_{n=1}^{N} \mathcal{N}\left(y_{n} \mid \boldsymbol{x}_{n} \cdot \boldsymbol{\beta}+c, \sigma^{2}\right)
$$

- Consider bias free case, $c=0$, otherwise include an additional column of ones in each $\boldsymbol{x}_{n}$.


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Equivalent graphical model

## Linear Regression

Maximum likelihood

- Taking the logarithm, we obtain

$$
\begin{aligned}
\ln p\left(\boldsymbol{y} \mid \boldsymbol{\beta}, \boldsymbol{X}, \sigma^{2}\right) & =\sum_{n=1}^{N} \ln \mathcal{N}\left(y_{n} \mid \boldsymbol{x}_{n} \cdot \boldsymbol{\beta}, \sigma^{2}\right) \\
& =-\frac{N}{2} \ln 2 \pi \sigma^{2}-\frac{1}{2 \sigma^{2}} \underbrace{\sum_{n=1}^{N}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)^{2}}_{\text {Sum of squares }}
\end{aligned}
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- The likelihood is maximized when the squared error is
- Least squares and maximum likelihood are equivalent.


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## Linear Regression and Least Squares


(C.M. Bishop, Pattern Recognition and Machine Learning)

$$
E(\boldsymbol{\beta})=\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)^{2}
$$

## Linear Regression and Least Squares

- Derivative w.r.t a single weight entry $\beta_{i}$

$$
\begin{aligned}
\frac{d}{\mathrm{~d} \beta_{i}} \ln p\left(\boldsymbol{y} \mid \boldsymbol{\beta}, \sigma^{2}\right) & =\frac{d}{\mathrm{~d} \beta_{i}}\left[-\frac{1}{2 \sigma^{2}} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)^{2}\right] \\
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- Set gradient w.r.t to $\boldsymbol{\beta}$ to zero

$$
\begin{aligned}
& \nabla_{\boldsymbol{\beta}} \ln p\left(\boldsymbol{y} \mid \boldsymbol{\beta}, \sigma^{2}\right)=\frac{1}{\sigma^{2}} \sum_{n=1}^{N} \boldsymbol{x}_{n}^{\top}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)=\mathbf{0} \\
& \Longrightarrow \boldsymbol{\beta}_{\mathrm{ML}}=\underbrace{\left(\boldsymbol{X}^{\top} \boldsymbol{X}\right)^{-1} \boldsymbol{X}^{\top}}_{\text {Pseudo inverse }} \boldsymbol{y}
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$$

- Here, the matrix $\boldsymbol{X}$ is defined as $\boldsymbol{X}=\left[\begin{array}{ccc}x_{1,1} & \ldots & x 1, D \\ \ldots & \ldots & \ldots \\ x_{N, 1} & \ldots & x_{N, D}\end{array}\right]$


## Polynomial Curve Fitting

Motivation

- Non-linear relationships.
- Multiple SNPs playing a role for a particular phenotype.



## Polynomial Curve Fitting

Univariate input $x$

- Use the polynomials up to degree $K$ to construct new features from $x$

$$
\begin{aligned}
f(x, \boldsymbol{\beta}) & =\beta_{0}+\beta_{1} x+\beta_{2} x^{2}+\cdots+\beta_{K} x^{K} \\
& =\sum_{k=1}^{K} \beta_{k} \phi_{k}(x)=\boldsymbol{\phi}(x) \boldsymbol{\beta}
\end{aligned}
$$

where we defined $\phi(x)=\left(1, x, x^{2}, \ldots, x^{K}\right)$.

(C.M. Bishop, Pattern Recognition and Machine Learning)

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$\phi$ can be any feature mapping:

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where $\sigma(a)=\frac{1}{1+\exp (-a)}$
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\phi_{j}(x)=\exp \left(-\frac{\left(x-\mu_{j}\right)^{2}}{2 s^{2}}\right)
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- Sigmoidal basis functions

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\phi_{j}(x)=\sigma\left(\frac{x-\mu_{j}}{s}\right), \quad \text { where } \sigma(a)=\frac{1}{1+\exp (-a)}
$$


(C.M. Bishop, Pattern Recognition and Machine Learning)

## Polynomial Curve Fitting

Overfitting

- The order of the polynomial $M$ is crucial to avoid under- and overfitting.

(C.M. Bishop, Pattern Recognition and Machine Learning)


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Overfitting

- The order of the polynomial $M$ is crucial to avoid under- and overfitting.
- Observation: Variance in regression coefficients $\boldsymbol{\beta}=\left[w_{0}^{\star}, \ldots, w_{9 \star}\right]$ grows dramatically with $M$

|  | $M=0$ | $M=1$ | $M=6$ | $M=9$ |
| ---: | ---: | ---: | ---: | ---: |
| $w_{0}^{\star}$ | 0.19 | 0.82 | 0.31 | 0.35 |
| $w_{1}^{\star}$ |  | -1.27 | 7.99 | 232.37 |
| $w_{2}^{\star}$ |  |  | -25.43 | -5321.83 |
| $w_{3}^{\star}$ |  |  | 17.37 | 48568.31 |
| $w_{4}^{\star}$ |  |  |  | -231639.30 |
| $w_{5}^{\star}$ |  |  |  | 640042.26 |
| $w_{6}^{\star}$ |  |  |  | -1061800.52 |
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(C.M. Bishop, Pattern Recognition and Machine Learning)

## Polynomial Curve Fitting

Generalization performance

$$
E(\boldsymbol{\beta})=\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)^{2}
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- Root-mean squared error

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\begin{aligned}
E_{\mathrm{RMS}} & =\sqrt{2 E(\boldsymbol{\beta}) / N} \\
& =\sqrt{\left(\sum_{n=1}^{N}\left(y_{n}-\boldsymbol{x}_{n} \cdot \boldsymbol{\beta}\right)^{2}\right) / N}
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- Underfitting: large $E_{\mathrm{RMS}}$ on train and test
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(C.M. Bishop, Pattern Recognition and Machine
- Underfitting: large $E_{\text {RMS }}$ on train and test data
- Overfitting: small $E_{\text {RMS }}$ on train and large $E_{\text {RMS }}$ on test data.


## Polynomial Curve Fitting

Overfitting

- The number $N$ of training data is crucial to accurately estimate many parameters without overfitting.

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## Multivariate regression

Polynomial curve fitting

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\begin{aligned}
f(x, \boldsymbol{\beta}) & =\beta_{0}+\beta_{1} x+\cdots+\beta_{K} x^{K} \\
& =\sum_{k=1}^{K} \beta_{k} \phi_{k}(x) \\
& =\phi(x) \cdot \boldsymbol{\beta}
\end{aligned}
$$

High dimensional regression

$$
\begin{aligned}
f(x, \boldsymbol{\beta}) & =\sum_{d=1}^{D} \beta_{d} x_{d} \\
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$$

- Note: When fitting a single binary variable $\boldsymbol{x}_{i}$, a linear model is most general!


## Regularized Least Squares

Ridge regression

- Solutions to avoid overfitting:

1. Intelligently choose number of parameters

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2. Get more data

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3. Regularize the regression weights $\boldsymbol{\beta}$

- Quadratically regularized objective function


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Ridge regression

- Solutions to avoid overfitting:

1. Intelligently choose number of parameters
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3. Regularize the regression weights $\boldsymbol{\beta}$

- Quadratically regularized objective function

$$
E(\boldsymbol{\beta})=\underbrace{\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}\right)^{2}}_{\text {Squared error }}+\underbrace{\frac{\lambda}{2} \boldsymbol{\beta}^{\top} \boldsymbol{\beta}}_{\text {Regularizer }}
$$

## Polynomial curve fitting

$L_{2}$ regularization

- $M=9$, different $\lambda$ values

(C.M. Bishop, Pattern Recognition and Machine Learning)


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## Polynomial curve fitting

$L_{2}$ regularization

- $M=9$, different $\lambda$ values

|  | $\ln \lambda=-\infty$ | $\ln \lambda=-18$ | $\ln \lambda=0$ |
| :--- | ---: | ---: | ---: |
| $w_{0}^{\star}$ | 0.35 | 0.35 | 0.13 |
| $w_{1}^{\star}$ | 232.37 | 4.74 | -0.05 |
| $w_{2}^{\star}$ | -5321.83 | -0.77 | -0.06 |
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## Bias-variance tradeoff

## Variance of $f^{\text {est }}$

## Bias of $f^{\text {est }}$

$$
\mathbb{E}_{\mathcal{D}}\left[f^{\text {est }}-\mathbb{E}\left[f^{\text {est }}\right]^{2}\right]
$$

$$
\mathbb{E}_{\mathcal{D}}\left[f^{\text {true }}-f^{\text {est }}\right]
$$

## Experiment:

- 100 rand $m$ data sets $(N=25)$
- learn 25 RBF basis functions
(C.M. Bishop, Pattern Recognition and Machine Learning)


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Estimated functions


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## Empirical Observations:

- Bias decreases with smaller $\lambda$


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## Empirical Observations:

- Bias decreases with smaller $\lambda$
- Variance increases with smaller $\lambda$


## Bias-variance tradeoff

Effect on mean squared error

$$
\begin{aligned}
& \qquad y_{n}=f^{\text {true }}\left(x_{n}\right)+\epsilon_{n} \\
& \text { mean squared error }\left(f^{\text {est }}\right)=\mathbb{E}_{\mathcal{D}}\left[\left(y-f^{\text {est }}(x)\right)^{2}\right] \\
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& =(\text { bias })^{2}+\text { variance }+ \text { noise }
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## Bias-variance tradeoff

Effect on mean squared error

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## Experiment as before:

- 100 random data sets $(N=25)$
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- vary $\lambda$
- Compute sample estimates of bias and
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(C.M. Bishop, Pattern Recognition and Machine Learning)


## Regularized Least Squares

More general regularizers

- More general regularization:

$$
E(\boldsymbol{\beta})=\underbrace{\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}\right)^{2}}_{\text {Squared error }}+\underbrace{\frac{\lambda}{2} \sum_{d=1}^{D}\left|\beta_{d}\right|^{q}}_{\text {Regularizer }}
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${ }^{-} q \leq 1$ : non-differentiable
$\rightarrow q<1$ : non-convex (could have local optima)

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## Smaller $q$ yields sparser solution $\boldsymbol{\beta}^{\star}$

- $q=2$ : Ridge regression $\left(L_{2}\right)$
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## Smaller $q$ yields sparser solution $\boldsymbol{\beta}^{\star}$

- $q=2$ : Ridge regression $\left(L_{2}\right)$
- $q=1$ : Lasso $\left(L_{1}\right)$
- Squared error
- Regularizer


(C.M. Bishop, Pattern Recognition and Machine Learning)


## Loss functions and related methods

- Even more general: general loss function

$$
E(\boldsymbol{\beta})=\underbrace{\frac{1}{2} \sum_{n=1}^{N} \mathcal{L}\left(y_{n}-\boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}\right)}_{\text {Loss }}+\underbrace{\frac{\lambda}{2} \sum_{d=1}^{D}\left|\beta_{d}\right|^{q}}_{\text {Regularizer }}
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- Q: How to determine $q$ and the a suitable loss function?


## Loss functions and related methods

Cross validation: minimization of expected loss

Compare candidate models $\mathcal{H}$ on generalization performance (different $\lambda$, different regularizers, different basis functions, etc.)

- Randomly split data into $K$ sets of equal size





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2. Test evaluation on $k^{\text {th }}$ set




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$\frac{1}{K} \sum_{k=1}^{K} E_{k}^{\mathrm{test}}(\mathcal{H})$





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- Pick model $\mathcal{H}$ with lowest average loss
- Re-train optimal $\mathcal{H}$ on all data


## Probabilistic interpretation

- So far: minimization of error functions.
- Back to probabilities?

$$
E(\boldsymbol{\beta})=\underbrace{\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}\right)^{2}}_{\text {Squared error }}+\underbrace{\frac{\lambda}{2} \boldsymbol{\beta}^{\top} \boldsymbol{\beta}}_{\text {Regularizer }}
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- Regularized regression equivalent to MAP estimation


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& =\text { const. }-\sum_{n=1}^{N} \ln \mathcal{N}\left(y_{n} \mid \boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}, \sigma^{2}\right)
\end{aligned} \quad-\ln \mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \frac{1}{\lambda} \boldsymbol{I}\right)
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E(\boldsymbol{\beta}) & =\underbrace{\frac{1}{2} \sum_{n=1}^{N}\left(y_{n}-\boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}\right)^{2}}_{\text {Squared error }} & +\underbrace{\frac{\lambda}{2} \boldsymbol{\beta}^{\top} \boldsymbol{\beta}}_{\text {Regularizer }} \\
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& =\text { const. }-\ln \underbrace{\ln \left(\boldsymbol{y} \mid \boldsymbol{\beta}, \boldsymbol{\Phi}(\boldsymbol{X}), \sigma^{2}\right)}_{\text {Likelihood }} & -\ln \underbrace{p(\boldsymbol{\beta})}_{\text {prior }}
\end{array}
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- Regularized regression equivalent to MAP estimation equivalent probabilistic representation in a similar way.


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- Regularized regression equivalent to MAP estimation
- Most alternative choices of regularizers and loss functions can be mapped to an equivalent probabilistic representation in a similar way.


## Outline

## Linear Regression II

Bayesian linear regression

## Model comparison and hypothesis testing

## Summary

## Bayesian linear regression

- Likelihood as before

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\prod_{n=1}^{N} \mathcal{N}\left(y_{n} \mid \boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}, \sigma^{2}\right)
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## Bayesian linear regression

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$$

- Define a conjugate prior over $\boldsymbol{\beta}$

$$
p(\boldsymbol{\beta})=\mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{m}_{0}, \boldsymbol{S}_{0}\right)
$$



## Bayesian linear regression

- Posterior probability of $\boldsymbol{\beta}$

$$
\begin{aligned}
p\left(\boldsymbol{\beta} \mid \boldsymbol{y}, \boldsymbol{X}, \sigma^{2}\right) & \propto \prod_{n=1}^{N} \mathcal{N}\left(y_{n} \mid \boldsymbol{\phi}\left(\boldsymbol{x}_{n}\right) \cdot \boldsymbol{\beta}, \sigma^{2}\right) \cdot \mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{m}_{0}, \boldsymbol{S}_{0}\right) \\
& =\mathcal{N}\left(\boldsymbol{y} \mid \boldsymbol{\Phi}(\boldsymbol{X}) \cdot \boldsymbol{\beta}, \sigma^{2} \boldsymbol{I}\right) \cdot \mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{m}_{0}, \boldsymbol{S}_{0}\right) \\
& =\mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{\mu}_{\boldsymbol{\beta}}, \boldsymbol{\Sigma}_{\boldsymbol{\beta}}\right)
\end{aligned}
$$

- where

$$
\begin{aligned}
\boldsymbol{\mu}_{\boldsymbol{\beta}} & =\boldsymbol{\Sigma}_{\boldsymbol{\beta}}\left(\boldsymbol{S}_{0}^{-1} \boldsymbol{m}_{0}+\frac{1}{\sigma^{2}} \boldsymbol{\Phi}(\boldsymbol{X})^{\top} \boldsymbol{y}\right) \\
\boldsymbol{\Sigma}_{\boldsymbol{\beta}} & =\left[\boldsymbol{S}_{0}^{-1}+\frac{1}{\sigma^{2}} \boldsymbol{\Phi}(\boldsymbol{X})^{\top} \boldsymbol{\Phi}(\boldsymbol{X})\right]^{-1}
\end{aligned}
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## Bayesian linear regression

## Prior choice

- Choice of prior: regularized (ridge) regression

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p(\boldsymbol{\beta})=\mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{m}_{0}, \boldsymbol{S}_{0}\right) .
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- In this case

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\boldsymbol{S}_{N}
\end{array}\right. \\
&=\left[\lambda \boldsymbol{I}+\frac{1}{\sigma^{2}} \boldsymbol{\Phi}(\boldsymbol{X})^{\top} \boldsymbol{\Phi}(\boldsymbol{X})\right]^{-1}
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(Exercise: derive both and compare!)


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- $\boldsymbol{m}_{N}$ is equal to the ridge regression ( $L_{2}$ ) estimate for $\boldsymbol{\beta}$ (Exercise: derive both and compare!)
- Equivalent to maximum likelihood estimate for $\lambda \rightarrow 0$ !


## Bayesian linear regression

## Example: sequential Bayesian learning

- likelihood

$$
\prod_{n=1}^{N} \mathcal{N}\left(y_{n} \mid \beta_{0}+x_{n} \beta_{1}, \sigma^{2}\right)
$$



- prior

$$
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- This prior is conjugate, so we can do sequential learning


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- 1 data point
- 2 data points
- 20 data points


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## Making predictions

- Prediction for fixed weight estimate $\hat{\boldsymbol{\beta}}$ at input $\boldsymbol{x}^{\star}$ trivial:

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p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \hat{\boldsymbol{\beta}}, \sigma^{2}\right)=\mathcal{N}\left(y^{\star} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \hat{\boldsymbol{\beta}}, \sigma^{2}\right)
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> Integrate over $\beta$ to take the posterior uncertainty into account

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p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \mathcal{D}\right) \propto \int_{\boldsymbol{\beta}} p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \boldsymbol{\beta}, \sigma^{2}\right) p\left(\boldsymbol{\beta} \mid \boldsymbol{X}, \boldsymbol{y}, \sigma^{2}\right) \mathrm{d} \boldsymbol{\beta}
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& \propto \int_{\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta}} \mathcal{N}\left(\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta} \mid y^{\star}, \sigma^{2}\right) \mathcal{N}\left(\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{m}_{N}, \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{S}_{N} \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)^{\top}\right)
\end{aligned}
$$

## Making predictions

- Prediction for fixed weight estimate $\hat{\boldsymbol{\beta}}$ at input $\boldsymbol{x}^{\star}$ trivial:

$$
p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \hat{\boldsymbol{\beta}}, \sigma^{2}\right)=\mathcal{N}\left(y^{\star} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \hat{\boldsymbol{\beta}}, \sigma^{2}\right)
$$

- Integrate over $\boldsymbol{\beta}$ to take the posterior uncertainty into account

$$
\begin{aligned}
& p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \mathcal{D}\right) \propto \int_{\boldsymbol{\beta}} p\left(y^{\star} \mid \boldsymbol{x}^{\star}, \boldsymbol{\beta}, \sigma^{2}\right) p\left(\boldsymbol{\beta} \mid \boldsymbol{X}, \boldsymbol{y}, \sigma^{2}\right) \mathrm{d} \boldsymbol{\beta} \\
& \propto \int_{\boldsymbol{\beta}} \mathcal{N}\left(y^{\star} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta}, \sigma^{2}\right) \mathcal{N}\left(\boldsymbol{\beta} \mid \boldsymbol{m}_{N}, \boldsymbol{S}_{N}\right) \\
& \propto \int_{\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta}} \mathcal{N}\left(\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta} \mid y^{\star}, \sigma^{2}\right) \mathcal{N}\left(\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{\beta} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{m}_{N}, \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \boldsymbol{S}_{N} \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)^{\top}\right) \\
& \propto \mathcal{N}\left(y^{\star} \mid \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right) \cdot \boldsymbol{m}_{N}, \sigma^{2}+\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)^{\top} \boldsymbol{S}_{N} \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)\right)
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$$

- Key:
- prediction is again Gaussian


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\end{aligned}
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- Key:
- prediction is again Gaussian
- Predictive variance is increased due to the posterior uncertainty in $\boldsymbol{\beta}$.


## Predictive distribution

Marginal variance for $x^{\star}$

$$
\sigma^{2}+\boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)^{\top} \boldsymbol{S}_{N} \boldsymbol{\phi}\left(\boldsymbol{x}^{\star}\right)
$$

## Predictive covariance

$$
\boldsymbol{\phi}(\boldsymbol{x})^{\top} \boldsymbol{S}_{N} \boldsymbol{\phi}\left(\boldsymbol{x}^{\prime}\right)
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## Experiment:

- 9 Gaussian basis functions


## Predictive distribution

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Visualize by sampling from the posterior of $\beta$


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- 9 Gaussian basis functions


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## Predictive covariance

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Visualize by sampling from the


Empirical Observations:

## Experiment:

- 9 Gaussian basis functions


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Visualize by sampling from the


Empirical Observations:

- Variance approaches noise variance for large sample size


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Visualize by sampling from the posterior of $\boldsymbol{\beta}$


Empirical Observations:

- Variance approaches noise variance for large sample size
- Co-variance between close $\boldsymbol{x}$ values is high


## Outline

## Linear Regression II

Bayesian linear regression

Model comparison and hypothesis testing

## Summary

## Model comparison

Motivation

- What degree of polynomials describes the data best?
- Is the linear model at all appropriate?


## Model comparison

Motivation

- What degree of polynomials describes the data best?
- Is the linear model at all appropriate?
- Association testing.



## Bayesian model comparison

- How do we choose among alternative models?
- Assume we want to choose among models $\mathcal{H}_{0}, \ldots, \mathcal{H}_{M}$ for a dataset $\mathcal{D}$.


Evidence Prior

## Bayesian model comparison

- How do we choose among alternative models?
- Assume we want to choose among models $\mathcal{H}_{0}, \ldots, \mathcal{H}_{M}$ for a dataset $\mathcal{D}$.
- Posterior probability for a particular model $i$

$$
p\left(\mathcal{H}_{i} \mid \mathcal{D}\right) \propto \underbrace{p\left(\mathcal{D} \mid \mathcal{H}_{i}\right)}_{\text {Evidence }} \underbrace{p\left(\mathcal{H}_{i}\right)}_{\text {Prior }}
$$

## Bayesian model comparison

How to calculate the evidence

- The evidence is not the model likelihood!

$$
p\left(\mathcal{D} \mid \mathcal{H}_{i}\right)=\int_{\boldsymbol{\Theta}} p(\mathcal{D} \mid \boldsymbol{\Theta}) p(\boldsymbol{\Theta}) \mathrm{d} \boldsymbol{\Theta} \text { for model parameters } \boldsymbol{\Theta}
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$$

- Remember:

$$
\begin{aligned}
p\left(\boldsymbol{\Theta} \mid \mathcal{H}_{i}, \mathcal{D}\right) & =\frac{p\left(\mathcal{D} \mid \mathcal{H}_{i}, \boldsymbol{\Theta}\right) p(\boldsymbol{\Theta})}{p\left(\mathcal{D} \mid \mathcal{H}_{i}\right)} \\
\text { posterior } & =\frac{\text { likelihood } \cdot \text { prior }}{\text { Evidence }}
\end{aligned}
$$

## Bayesian model comparison

Bayesian Occam's razor

- The evidence integral penalizes overly complex models.

A model with few parameters and lower maximum likelihood $\left(\mathcal{H}_{1}\right)$ may win over a model with a peaked likelihood that requires many more parameters $\left(\mathcal{H}_{2}\right)$. When averaging the likelihood over all possible parameters, more complex models have low fit for most of the setting, resulting in a lower evidence

(C.M. Bishop, Pattern Recognition and Machine Learning)

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- Complex models have low average over many possible data sets

(C.M. Bishop, Pattern Recognition and Machine

[^0]- Simple models have large evidence on a small range of data sets, extremely low evidence otherwise


## Application to GWAS

Relevance of a single SNP

- Consider an association study.
- $\mathcal{H}_{0}$ : no association

$$
\begin{aligned}
p\left(\boldsymbol{y} \mid \mathcal{H}_{0}, \boldsymbol{X}, \boldsymbol{\Theta}_{0}\right) & =\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma^{2} \boldsymbol{I}\right) \\
p\left(\mathcal{D} \mid \mathcal{H}_{0}\right) & =\int_{\sigma^{2}} \mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma^{2} \boldsymbol{I}\right) p\left(\sigma^{2}\right)
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Depending on the choice of priors, $p\left(\sigma^{2}\right)$ and $p(\beta)$, the required integrals are often tractable in closed form. (Conjugate priors!)

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- $\mathcal{H}_{1}$ : linear association

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p\left(\boldsymbol{y} \mid \mathcal{H}_{1}, \boldsymbol{x}_{i}, \boldsymbol{\Theta}_{1}\right) & =\mathcal{N}\left(\boldsymbol{y} \mid \boldsymbol{x}_{i} \cdot \beta, \sigma^{2} \boldsymbol{I}\right) \\
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Scoring models

- Similar to likelihood ratios, the ratio of the evidences, the Bayes factor can be used to score alternative models:

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B F=\ln \frac{p\left(\mathcal{D} \mid \mathcal{H}_{1}\right)}{p\left(\mathcal{D} \mid \mathcal{H}_{0}\right)}
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## Application to GWAS

Posterior probability of an association

- Bayes factors are useful, however we would like a probabilistic answer how certain an association really is.


## $p\left(\mathcal{H}_{1} \mid \mathcal{D}\right)+p\left(\mathcal{H}_{0} \mid \mathcal{D}\right)=1$, prior probability of observing a real

association.

## Application to GWAS

## Posterior probability of an association

- Bayes factors are useful, however we would like a probabilistic answer how certain an association really is.
- Posterior probability of $\mathcal{H}_{1}$

$$
\begin{aligned}
p\left(\mathcal{H}_{1} \mid \mathcal{D}\right) & =\frac{p\left(\mathcal{D} \mid \mathcal{H}_{1}\right) p\left(\mathcal{H}_{1}\right)}{p(\mathcal{D})} \\
& =\frac{p\left(\mathcal{D} \mid \mathcal{H}_{1}\right) p\left(\mathcal{H}_{1}\right)}{p\left(\mathcal{D} \mid \mathcal{H}_{1}\right) p\left(\mathcal{H}_{1}\right)+p\left(\mathcal{D} \mid \mathcal{H}_{0}\right) p\left(\mathcal{H}_{0}\right)}
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## Bayes factor versus likelihood ratio

Bayes factor

- Models of different complexity can be objectively compared.
- Statistical significance as posterior probability of a model.


## Likelihood ratio

- Likelihood ratio scales with the number of parameters.
- Likelihood ratios have known null distribution, yielding p-values.


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## Marginal likelihood of variance component models

- Consider a linear model, accounting for a set of measured SNPs $\boldsymbol{X}$

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \sum_{s=1}^{S} \boldsymbol{x}_{s} \beta_{s}, \sigma^{2} \boldsymbol{I}\right)
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- Choose identical Gaussian prior for all weights

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p(\boldsymbol{\beta})=\prod_{s=1}^{S} \mathcal{N}\left(\beta_{s} \mid 0, \sigma_{\mathrm{g}}^{2}\right)
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\end{aligned}
$$

- Number of hyperparameters independent of number of SNPs


## Marginal likelihood of variance component models

## Basis functions

- The analogous derivation can be repeated for a feature mapping $\phi$

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \sum_{s=1}^{S} \phi\left(\boldsymbol{x}_{s}\right) \beta_{s}, \sigma^{2} \boldsymbol{I}\right)=
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$$
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- Marginal likelihood

$$
\begin{aligned}
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma^{2}, \sigma_{\mathrm{g}}^{2}\right) & =\int_{\boldsymbol{\beta}} \mathcal{N}\left(\boldsymbol{y} \mid \boldsymbol{\Phi}(\boldsymbol{X}) \boldsymbol{\beta}, \sigma^{2} \boldsymbol{I}\right) \mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \boldsymbol{I}\right) \\
& =\mathcal{N}(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \underbrace{\boldsymbol{\Phi}(\boldsymbol{X}) \boldsymbol{\Phi}(\boldsymbol{X})^{\top}}_{\boldsymbol{K}}+\sigma^{2} \boldsymbol{I})
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p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \sum_{s=1}^{S} \phi\left(\boldsymbol{x}_{s}\right) \beta_{s}, \sigma^{2} \boldsymbol{I}\right)=
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\end{aligned}
$$

- $\boldsymbol{K}:(\mathrm{N} \times \mathrm{N})$ kernel or covariance induced by feature mapping $\phi$.


## Marginal likelihood of variance component models

Application to GWAS

The missing heritability paradox

- Complex traits are regulated by a large number of small effects
- Human height: the best single SNP explains little variance.
- But: height of the parents are highly predictive for the height of the child!


## Marginal likelihood of variance component models

Application to GWAS
Linear additive models for complex traits

- Multiple linear regression model over causal SNPs

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \sum_{s \in \text { causal }} \boldsymbol{x}_{s} \beta_{s}, \sigma^{2} \boldsymbol{I}\right)
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- Which SNPs are causal ?

Approximation: consider all $S$ available common SNPs [Yang et al. 2011]

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p\left(\boldsymbol{y} \mid \boldsymbol{X}, \boldsymbol{\beta}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \sum_{s=1}^{S} \boldsymbol{x}_{s} \beta_{s}, \sigma^{2} \boldsymbol{I}\right)
$$

- Causal SNPs either in the model or "tagged" by linkage disequilibrium to nearby common SNPs
- Marginalize out weights


## Marginal likelihood of variance component models

## Application to GWAS

Linear additive models for complex traits

- Multiple linear regression model over causal SNPs

$$
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$$

- Which SNPs are causal ?

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$$

- Causal SNPs either in the model or "tagged" by linkage disequilibrium to nearby common SNPs
- Uncertainty over causal SNPs: Prior on all SNP effects $p\left(\beta_{s}\right)=\mathcal{N}\left(\beta_{s} \mid 0, \sigma_{\mathrm{g}}^{2} / S\right)$
- Marginalize out weights

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma_{\mathrm{g}}^{2}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \sum_{s=1}^{S} \frac{1}{S} \boldsymbol{x}_{s} \boldsymbol{x}_{s}^{\top}+\sigma^{2} \boldsymbol{I}\right)
$$

## Marginal likelihood of variance component models

## Application to GWAS

Linear additive models for complex traits

- Multiple linear regression model over causal SNPs

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$$

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$$

- Perform maximum marginal likelihood estimation on $\sigma_{\mathrm{g}}^{2}$ and $\sigma^{2}$.


## Marginal likelihood of variance component models

Application to GWAS

- Approximate variance model

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma_{\mathrm{g}}^{2}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \frac{1}{S} \boldsymbol{X} \boldsymbol{X}^{\top}+\sigma^{2} \boldsymbol{I}\right)
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## Marginal likelihood of variance component models

Application to GWAS

- Approximate variance model
$p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma_{\mathrm{g}}^{2}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \frac{1}{S} \boldsymbol{X} \boldsymbol{X}^{\top}+\sigma^{2} \boldsymbol{I}\right)$
- Genetic variance $\sigma_{\mathrm{g}}^{2}$ across chromosomes




Narrow-sense refers to linear additive nart of the heritability

## Marginal likelihood of variance component models

Application to GWAS

- Approximate variance model
$p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma_{\mathrm{g}}^{2}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \frac{1}{S} \boldsymbol{X} \boldsymbol{X}^{\top}+\sigma^{2} \boldsymbol{I}\right)$
- Genetic variance $\sigma_{\mathrm{g}}^{2}$ across chromosomes
- (Narrow-sense) heritability

$$
h^{2}=\frac{\sigma_{\mathrm{g}}^{2}}{\sigma_{\mathrm{g}}^{2}+\sigma^{2}}
$$





## Marginal likelihood of variance component models

Application to GWAS

- Approximate variance model

$$
p\left(\boldsymbol{y} \mid \boldsymbol{X}, \sigma_{\mathrm{g}}^{2}, \sigma^{2}\right)=\mathcal{N}\left(\boldsymbol{y} \mid \mathbf{0}, \sigma_{\mathrm{g}}^{2} \frac{1}{S} \boldsymbol{X} \boldsymbol{X}^{\top}+\sigma^{2} \boldsymbol{I}\right)
$$

- Genetic variance $\sigma_{\mathrm{g}}^{2}$ across chromosomes
- (Narrow-sense) heritability

$$
h^{2}=\frac{\sigma_{\mathrm{g}}^{2}}{\sigma_{\mathrm{g}}^{2}+\sigma^{2}}
$$





- Narrow-sense refers to linear additive part of the heritability


## Outline

```
Linear Regression II
Bayesian linear regression
```


## Model comparison and hypothesis testing

Summary

## Summary

- Linear models for curve fitting and multiple linear regression.
- Maximum likelihood and least squares regression are identical.
- Construction of features using a mapping $\phi$.
- Regularized least squares and other models that correspond to different choices of loss functions.
- Bayesian linear regression.
- Model comparison and Occam's razor.
- Variance component models in GWAS.


## Outlook

- Estimation technique for $\sigma_{\mathrm{g}}^{2}$ and $\sigma^{2}$.
- Use marginal linear model for confounder correction in GWAS testing of single SNPs
- Linear mixed models for GWAS testing
- Use marginal linear model for testing for significant associations of sets of variants.
- Idea : Test for $\mathcal{H}_{0}: \sigma_{\mathrm{g}}^{2}=0$ vs. $\mathcal{H}_{1}: \sigma_{\mathrm{g}}^{2}>0$
- Random effects testing


## Tasks

- Derive ridge regularized $\boldsymbol{\beta}_{\text {MAP }}$ in linear regression
- Derive posterior distribution (mean and covariance) of $\boldsymbol{\beta}$ in a linear regression under a Normal prior
- Compare them!
- Derive marginal likelihood for linear regression under a Normal prior on $\boldsymbol{\beta}$
- hint: The following expression is a Gaussian convolution:

$$
\begin{aligned}
& \int \mathcal{N}\left(\boldsymbol{a} \mid \boldsymbol{b}, \boldsymbol{\Sigma}_{\boldsymbol{a}}\right) \cdot \mathcal{N}\left(\boldsymbol{b} \mid \boldsymbol{\mu}_{\boldsymbol{b}}, \boldsymbol{\Sigma}_{\boldsymbol{b}}\right) \mathrm{d} \boldsymbol{b} \\
= & \int \mathcal{N}\left(\boldsymbol{a}-\boldsymbol{b} \mid \mathbf{0}, \boldsymbol{\Sigma}_{\boldsymbol{a}}\right) \cdot \mathcal{N}\left(\boldsymbol{b} \mid \boldsymbol{\mu}_{\boldsymbol{b}}, \boldsymbol{\Sigma}_{\boldsymbol{b}}\right) \mathrm{d} \boldsymbol{b}
\end{aligned}
$$


[^0]:    Learning)

