



Bayesian Statistics for Genetics

Lecture 4: Linear models

July, 2020

In this session

- An important conjugacy result – Normal prior, Normal likelihood
- Linear regression – the standard approach for continuous outcomes (this material mostly review?)
- Bayesian linear regression
- A first look at Markov Chain Monte Carlo – much more in later sessions

Normal prior, Normal likelihood

The best-known and most widely-used statistical is the *Normal* or *Gaussian* distribution, denoted $N(\mu, \sigma^2)$ for mean μ and variance σ^2 .

In sampling distributions, approximately Normal observations are expected when the variable is the sum of many similarly-sized small influences (e.g. height as a sum of SNP effects). This is called the *Central Limit Theorem*.



In priors, Normals are a convenient way to state beliefs, mainly because they're so familiar. They can also make some calculations easier (which is why Gauss liked them).

Normal prior, Normal likelihood: conjugacy

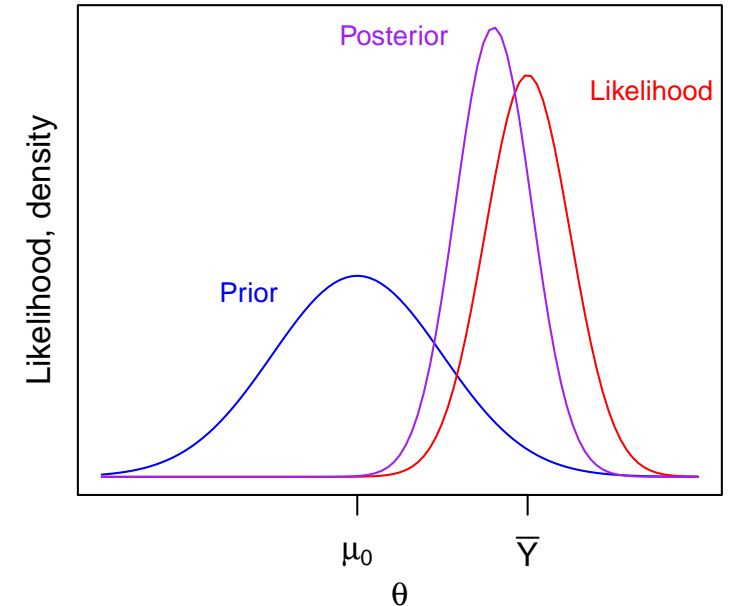
If Y_1, \dots, Y_n are a random sample from $N(\theta, \sigma^2)$ with known variance σ^2 :

prior $\theta \sim N(\mu_0, \tau^2)$

sampling model $Y \sim N(\theta, \sigma^2)$

then posterior $\theta|Y \sim N\left(w\bar{Y} + (1-w)\mu_0, \frac{1}{\frac{1}{\tau^2} + \frac{n}{\sigma^2}}\right)$

where $w = \frac{\frac{n}{\sigma^2}}{\frac{1}{\tau^2} + \frac{n}{\sigma^2}}$



- Posterior mean is a weighted average of prior mean and sample mean
- Weights are \propto precision, i.e. $1/\text{variance}$.
- Posterior precision = prior precision + precision from data
- With large n Bayes gives essentially standard result: point estimate \bar{Y} , 95% interval is $\bar{Y} \pm 1.96\sigma/\sqrt{n}$. With tiny n , posterior \approx prior.

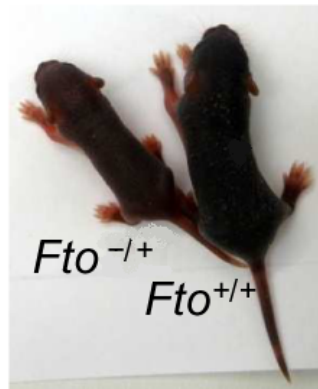
FTO example: design

We'll soon use a version of Normal/Normal conjugacy in an analysis of the FTO gene, involved in growth and obesity.

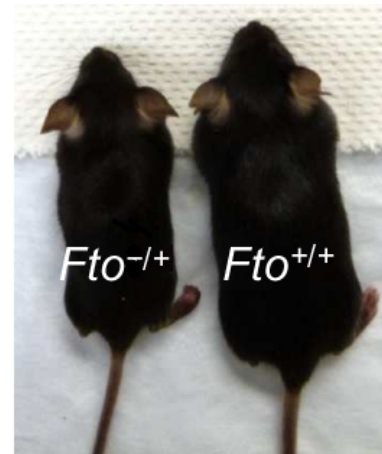
Experimental design:

- 10 *fto* $+/-$ mice
- 10 *fto* $-/-$ mice
- Mice are sacrificed at the end of 1-5 weeks of age (not 16 weeks, as here)
- Two mice in each group are sacrificed at each age
- $n = 20$ overall, so a small but well-controlled study

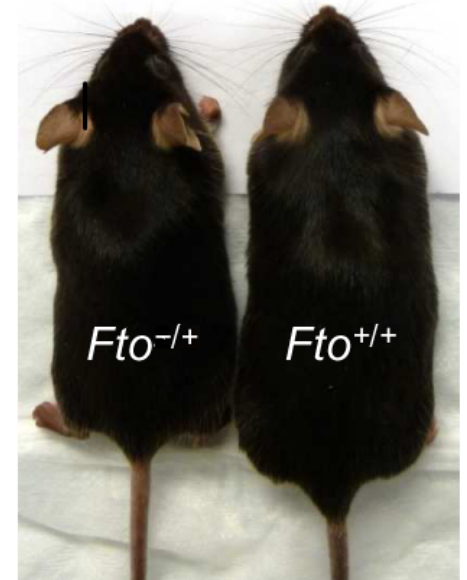
Postnatal day 5



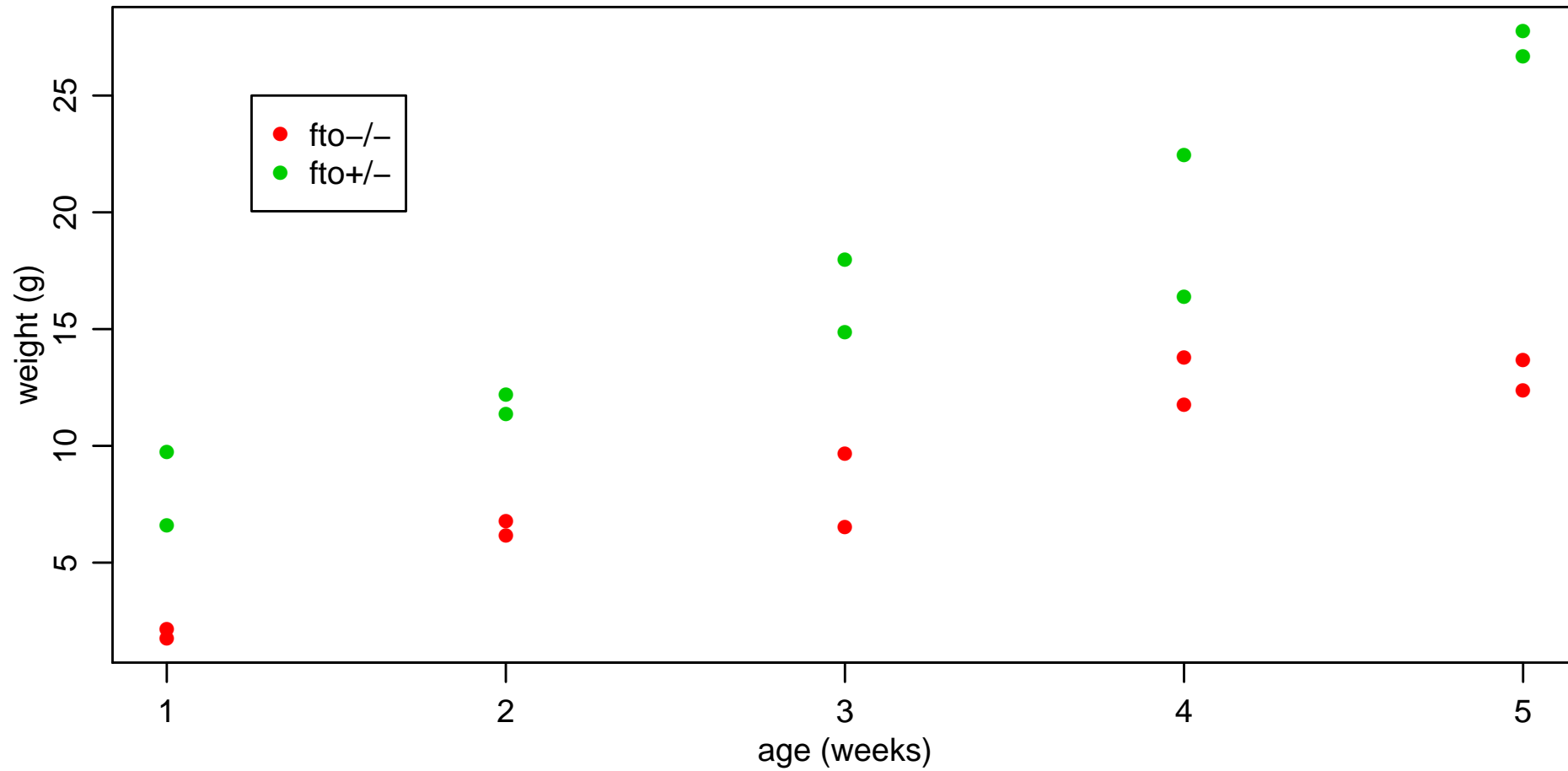
4-week-old



16-week-old



FTO example: data



FTO example: critical modeling assumption

In this example:

- Y = weight, which will be Normal **conditional** on covariate-specific mean
- x_g = indicator of fto heterozygote $\in \{0, 1\}$ = number of “+” alleles
- x_a = age in weeks $\in \{1, 2, 3, 4, 5\}$

The critical modeling choice is how mean Y depends on the covariates. Without further assumptions, we could choose to model $\mathbb{E}[Y|X = x]$ as

genotype	age (weeks)				
	1	2	3	4	5
−/−	$\theta_{0,1}$	$\theta_{0,2}$	$\theta_{0,3}$	$\theta_{0,4}$	$\theta_{0,5}$
+/−	$\theta_{1,1}$	$\theta_{1,2}$	$\theta_{1,3}$	$\theta_{1,4}$	$\theta_{1,5}$

This can't be ‘wrong’ – there *is* a mean weight for each genotype at each age – but we'd need to estimate 10 parameters from $n = 20$ data points.

Linear regression

But pragmatically, we instead assume smoothness in mean weight as a function of age. For each group, we assume

$$\mathbb{E}[Y|X_a = x_a] = \alpha_0 + \alpha_1 x_a$$

for some unknown α_0 and α_1 , that we'll estimate.

- Now we can *borrow strength* across the ages. For example, the difference in 4-5 week mice weights tells us about the difference in 1-2 week weights
- Can also write the assumption as

$$y = \alpha_0 + \alpha_1 x_a + \epsilon,$$

where ϵ is some mean-zero 'noise'

- A more complex linear regression might assume e.g. $y = \alpha_0 + \alpha_1 x_a + \alpha_2 x_a^2 + \alpha_3 x_a^3 + \epsilon$, — linearity means “linear in the parameters”, i.e. adding several covariates, each multiplied by its own α coefficient.

Multiple linear regression

We can also create variables, to describe models for both groups simultaneously:

$$x_{i,1} = 1 \text{ for each subject } i$$

$$x_{i,2} = 0 \text{ if subject } i \text{ is homozygous, } 1 \text{ if heterozygous}$$

$$x_{i,3} = \text{age of subject } i, \text{ in weeks}$$

$$x_{i,4} = x_{i,2} \times x_{i,3}$$

$$\mathbb{E}[Y_i | \mathbf{X} = \mathbf{x}] = \beta_1 x_{i,1} + \beta_2 x_{i,2} + \beta_3 x_{i,3} + \beta_4 x_{i,4},$$

$$\dots \text{or write this as } Y_i = \beta_1 x_{i,1} + \beta_2 x_{i,2} + \beta_3 x_{i,3} + \beta_4 x_{i,4} + \epsilon_i$$

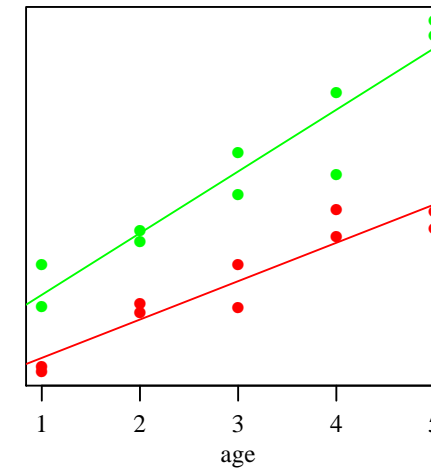
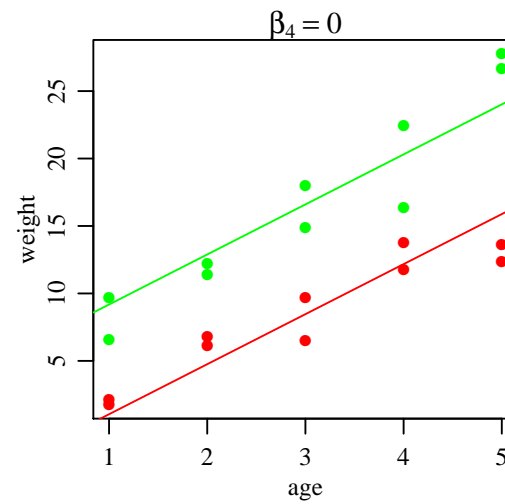
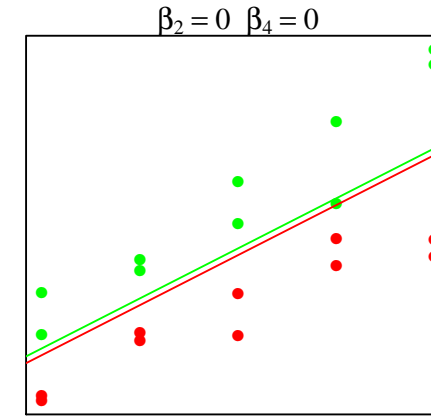
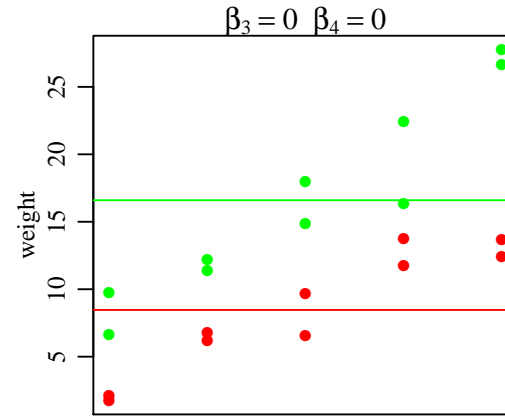
for some mean-zero ϵ_i . Note that under this model,

$$\mathbb{E}[Y | \mathbf{x},] = \beta_1 + \beta_3 \times \text{age} \quad \text{if } x_2 = 0, \text{ and}$$

$$\mathbb{E}[Y | \mathbf{x}] = (\beta_1 + \beta_2) + (\beta_3 + \beta_4) \times \text{age} \quad \text{if } x_2 = 1.$$

Multiple linear regression

For graphical thinkers...



Normal linear regression

How do the Y_i vary around $\mathbb{E}[Y_i|\beta, x_i]$, ?

$$Y_i = \beta^T x_i + \epsilon_i$$
$$\epsilon_1, \dots, \epsilon_n \sim \text{i.i.d. Normal}(0, \sigma^2).$$

Assuming independent identically-distributed Normal errors gives the likelihood:

$$p(y_1, \dots, y_n | x_1, \dots, x_n, \beta, \sigma^2) = \prod_{i=1}^n p(y_i | x_i, \beta, \sigma^2)$$
$$= (2\pi\sigma^2)^{-n/2} \exp \left(-\frac{1}{2\sigma^2} \sum_{i=1}^n (y_i - \beta^T x_i)^2 \right).$$

Note: in large(r) sample sizes, what we learn about the β_j is “robust” to the Normality assumption—but with $n = 20$ we do **rely** on the mean being linear in the x ’s, and on the ϵ_i ’s variance σ^2 being constant with respect to x .



Linear regression: non-Bayes methods (*)

What values of β are consistent with our data \mathbf{y}, \mathbf{X} ? Recall that

$$p(y_1, \dots, y_n | x_1, \dots, x_n, \beta, \sigma^2) = (2\pi\sigma^2)^{-n/2} \exp\left\{-\frac{1}{2\sigma^2} \sum_{i=1}^n (y_i - \beta^T x_i)^2\right\}.$$

This is big when $\text{SSR}(\beta) = \sum (y_i - \beta^T x_i)^2$ is small. It can also be written as

$$\text{SSR}(\beta) = \sum_{i=1}^n (y_i - \beta^T x_i)^2 = (\mathbf{y} - \mathbf{X}\beta)^T (\mathbf{y} - \mathbf{X}\beta) = \mathbf{y}^T \mathbf{y} - 2\beta^T \mathbf{X}^T \mathbf{y} + \beta^T \mathbf{X}^T \mathbf{X} \beta,$$

where we use matrix notation, i.e.

$$\mathbf{y} = \begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{pmatrix}, \mathbf{X}\beta = \begin{pmatrix} \mathbf{x}_1 \rightarrow \\ \mathbf{x}_2 \rightarrow \\ \vdots \\ \mathbf{x}_n \rightarrow \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{pmatrix} = \begin{pmatrix} \mathbf{x}_1^T \beta \\ \mathbf{x}_2^T \beta \\ \vdots \\ \mathbf{x}_n^T \beta \end{pmatrix} = \begin{pmatrix} \beta_1 x_{1,1} + \dots + \beta_p x_{1,p} \\ \beta_2 x_{2,1} + \dots + \beta_p x_{2,p} \\ \vdots \\ \beta_1 x_{n,1} + \dots + \beta_p x_{n,p} \end{pmatrix}.$$

Linear regression: non-Bayes methods (*, almost)

Classical linear regression uses the $\hat{\beta}$ that makes SSR smallest, i.e. finds the 'best-fitting' model. To minimize SSR, 'recall' that...

1. a minimum of a function $g(z)$ occurs at a value z such that $\frac{d}{dz}g(z) = 0$;
2. the derivative of $g(z) = az$ is a and the derivative of $g(z) = bz^2$ is $2bz$.

Doing this for SSR...

$$\begin{aligned}\frac{d}{d\beta} \text{SSR}(\beta) &= \frac{d}{d\beta} (y^T y - 2\beta^T X^T y + \beta^T X^T X \beta) \\ &= -2X^T y + 2X^T X \beta , \\ \text{and so } \frac{d}{d\beta} \text{SSR}(\beta) = 0 &\Leftrightarrow -2X^T y + 2X^T X \beta = 0 \\ &\Leftrightarrow X^T X \beta = X^T y \Leftrightarrow \beta = (X^T X)^{-1} X^T y .\end{aligned}$$

$\hat{\beta}_{\text{ols}} = (X^T X)^{-1} X^T y$ is the *Ordinary Least Squares* (OLS) estimator of β .

Linear regression: non-Bayes methods in R

OLS estimate

```
> beta.ols <- solve( t(X)%*%X )%*%t(X)%*%y
```

```
> beta.ols
```

```
      [,1]
```

```
(Intercept) -0.06821632
```

```
xg          2.94485495
```

```
xa          2.84420729
```

```
xg:xa       1.72947648
```

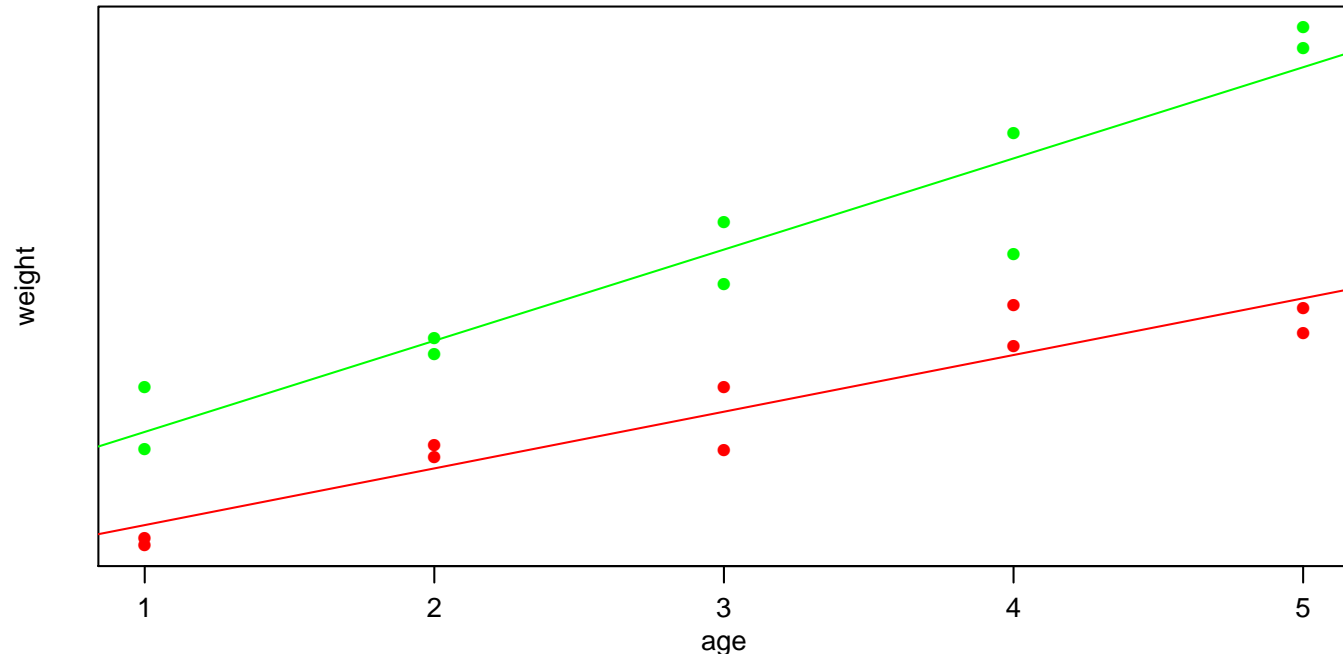
or less painfully, using `lm()` and R's formula syntax:

```
> fit.ols<-lm( y~ xg*xa )
```

```
> coef( summary(fit.ols) )
```

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	-0.06821632	1.4222970	-0.04796208	9.623401e-01
xg	2.94485495	2.0114316	1.46405917	1.625482e-01
xa	2.84420729	0.4288387	6.63234803	5.760923e-06
xg:xa	1.72947648	0.6064695	2.85171239	1.154001e-02

Linear regression: non-Bayes methods in R



(The classic version estimates the standard error of each $\hat{\beta}_j$, and gives p -values indicating how significantly they differ from zero. t_j denotes $\hat{\beta}_j / \text{Est.StdErr}[\hat{\beta}_j]$, which has a t distribution if $\beta_j = 0$.)

```
> coef( summary(fit.ols) )
```

	Estimate	Std. Error	t value	Pr(> t)
(Intercept)	-0.06821632	1.4222970	-0.04796208	9.623401e-01
xg	2.94485495	2.0114316	1.46405917	1.625482e-01
xa	2.84420729	0.4288387	6.63234803	5.760923e-06
xg:xa	1.72947648	0.6064695	2.85171239	1.154001e-02

Multivariate Normal distribution

Before Bayesian linear regression, a final piece of math notation.

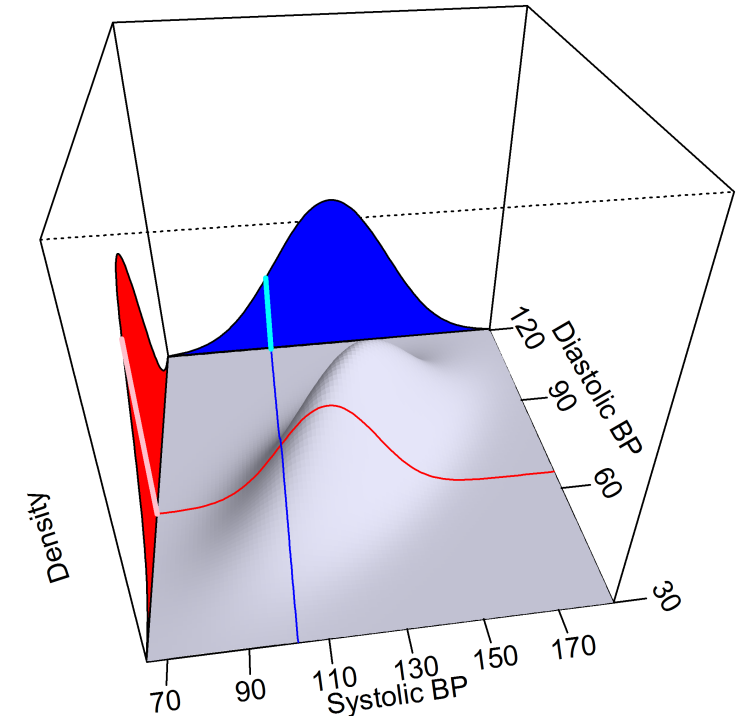
The *multivariate Normal* distribution describes random vectors. For mean \mathbf{m} and variance matrix* \mathbf{V} , it is written $\text{mvn}(\mathbf{m}, \mathbf{V})$ – see right for an example:

So we can write a full linear regression model as just

$$\mathbf{y}|\mathbf{X}, \boldsymbol{\beta}, \sigma^2 \sim \text{mvn}(\mathbf{X}\boldsymbol{\beta}, \sigma^2 \mathbf{I}),$$

where σ^2 is the (assumed-constant) variance of each observation around its mean, and \mathbf{I} denotes an *identity* matrix, with 1s on the diagonal and 0 elsewhere.

* For random vector \mathbf{Y}_i , variance matrix $\text{Var}[\mathbf{Y}]$ has diagonal elements $\text{Var}[Y_i]$ and off diagonal elements $\text{Cov}[Y_i, Y_j]$



Bayesian inference for linear regression models

With σ^2 known, Normal priors for β are conjugate. With

prior	β	\sim	$\text{mvn}(\beta_0, \Sigma_0)$
sampling model	y	\sim	$\text{mvn}(\mathbf{X}\beta, \sigma^2\mathbf{I})$

then posterior $\beta|y, \mathbf{X}$ \sim $\text{mvn}(\beta_n, \Sigma_n)$,
where $\Sigma_n = \text{Var}\beta|y, \mathbf{X}, \sigma^2 = (\Sigma_0^{-1} + \mathbf{X}^T\mathbf{X}/\sigma^2)^{-1}$
 $\beta_n = \mathbb{E}\beta|y, \mathbf{X}, \sigma^2 = (\Sigma_0^{-1} + \mathbf{X}^T\mathbf{X}/\sigma^2)^{-1}(\Sigma_0^{-1}\beta_0 + \mathbf{X}^T y/\sigma^2).$

- Posterior precision (inverse-variance) is the sum of precision from prior and sampling model
- Posterior mean is a kind of weighted average of prior mean on $\hat{\beta}_{OLS}$, with precision/inverse-variance weights
- If $\Sigma_0^{-1} \ll \mathbf{X}^T\mathbf{X}/\sigma^2$, then $\beta_n \approx \hat{\beta}_{ols}$, if $\Sigma_0^{-1} \gg \mathbf{X}^T\mathbf{X}/\sigma^2$, then $\beta_n \approx \beta_0$ – sensibly

The g -prior

But how to pick β_0, Σ_0 ? A classical suggestion (Zellner, 1986) uses the g -prior:

$$\beta \sim \text{mvn}(\mathbf{0}, g\sigma^2(\mathbf{X}^T\mathbf{X})^{-1}).$$

Why this variance? The variance of the OLS estimate $\hat{\beta}_{\text{ols}}$ is

$$\text{Var}\hat{\beta}_{\text{ols}} = \sigma^2(\mathbf{X}^T\mathbf{X})^{-1} = \frac{\sigma^2}{n}(\mathbf{X}^T\mathbf{X}/n)^{-1},$$

which can be thought of as (roughly) the uncertainty in β from n observations. In the g -prior the variance is

$$g\sigma^2(\mathbf{X}^T\mathbf{X})^{-1} = \frac{\sigma^2}{n/g}(\mathbf{X}^T\mathbf{X}/n)^{-1},$$

which can be viewed as the uncertainty from n/g observations.

For example, $g = n$ means the prior has the same amount of info as 1 observation – so (roughly!) not much, in a large study.

Posterior distributions under the g -prior

Following the conjugacy results, with σ^2 known it turns out that

$$\boldsymbol{\beta}|\mathbf{y}, \mathbf{X}, \sigma^2 \sim \text{mvn}(\boldsymbol{\beta}_n, \boldsymbol{\Sigma}_n),$$

$$\begin{aligned} \text{where } \boldsymbol{\Sigma}_n = \text{Var}[\boldsymbol{\beta}|\mathbf{y}, \mathbf{X}, \sigma^2] &= \frac{g}{g+1} \sigma^2 (\mathbf{X}^T \mathbf{X})^{-1} \\ \boldsymbol{\beta}_n = \mathbb{E}[\boldsymbol{\beta}|\mathbf{y}, \mathbf{X}, \sigma^2] &= \frac{g}{g+1} (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{y} \end{aligned}$$

- The posterior mean estimate $\boldsymbol{\beta}_n$ is simply $\frac{g}{g+1} \hat{\boldsymbol{\beta}}_{\text{ols}}$.
- The posterior variance of $\boldsymbol{\beta}$ is simply $\frac{g}{g+1} \text{Var}[\hat{\boldsymbol{\beta}}_{\text{ols}}]$.
- $\boldsymbol{\beta}_n^T \boldsymbol{\Sigma}_n^{-1} \boldsymbol{\beta}_n$ is $\frac{g}{g+1}$ times smaller than $\hat{\boldsymbol{\beta}}_{OLS}^T \text{Var}[\hat{\boldsymbol{\beta}}_{OLS}]^{-1} \hat{\boldsymbol{\beta}}_{OLS}$, the usual signal-to-noise measure we turn into p -values
- g shrinks the coefficients towards $\mathbf{0}$ and so can prevent overfitting to the data
- If $g \propto n$, then as n increases, inference approximates classical methods.

Monte Carlo simulation

But σ^2 is rarely known exactly, so more realistic analysis captures that uncertainty via a prior. A convenient & popular choice is the *inverse-Gamma* distribution:

prior	$1/\sigma^2 \sim \text{gamma}(\nu_0/2, \nu_0\sigma_0^2/2)$
sampling model	$\mathbf{y} \sim \text{mvn}(\mathbf{X}\boldsymbol{\beta}, \sigma^2\mathbf{I})$
posterior	$1/\sigma^2 \mathbf{y}, \mathbf{X} \sim \text{gamma}([\nu_0 + n]/2, [\nu_0\sigma_0^2 + \text{SSR}_g]/2)$

...where SSR_g is complicated but basically a sum of squared residuals.

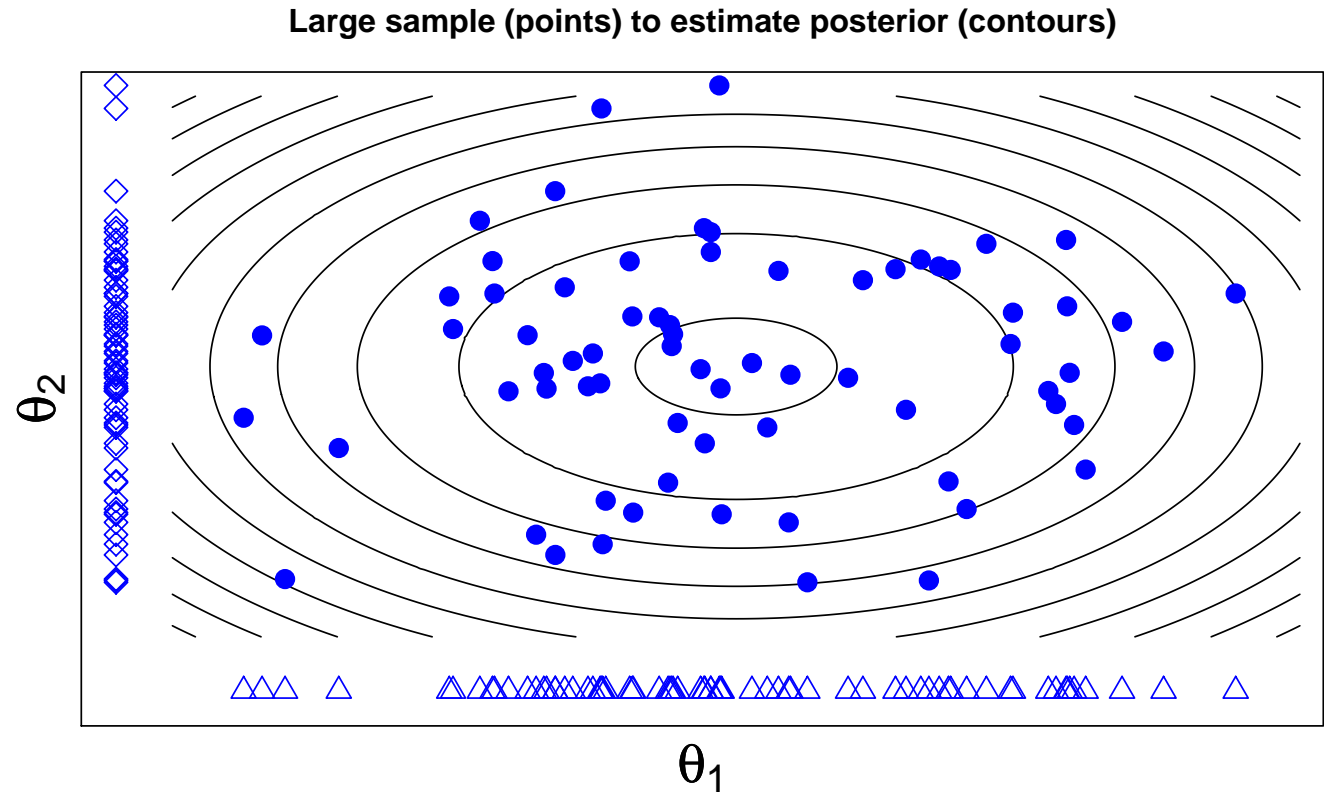
A natural next step is be to use the conjugate posteriors for σ and $\boldsymbol{\beta}$ together – usually to get the marginal posterior for $\boldsymbol{\beta}$. But this requires integration:

$$p(\boldsymbol{\beta}|\mathbf{y}, \mathbf{X}) = \int_{\sigma^2 > 0} p(\boldsymbol{\beta}, \sigma^2|\mathbf{y}, \mathbf{X}) d\sigma^2 = \int_{\sigma^2 > 0} p(\boldsymbol{\beta}|\sigma^2, \mathbf{y}, \mathbf{X}) p(\sigma^2|\mathbf{y}, \mathbf{X}) d\sigma^2$$

This takes work, and is error-prone. Instead we'll use Monte Carlo methods.

Monte Carlo simulation

The *Monte Carlo method* is important for Bayesian work;

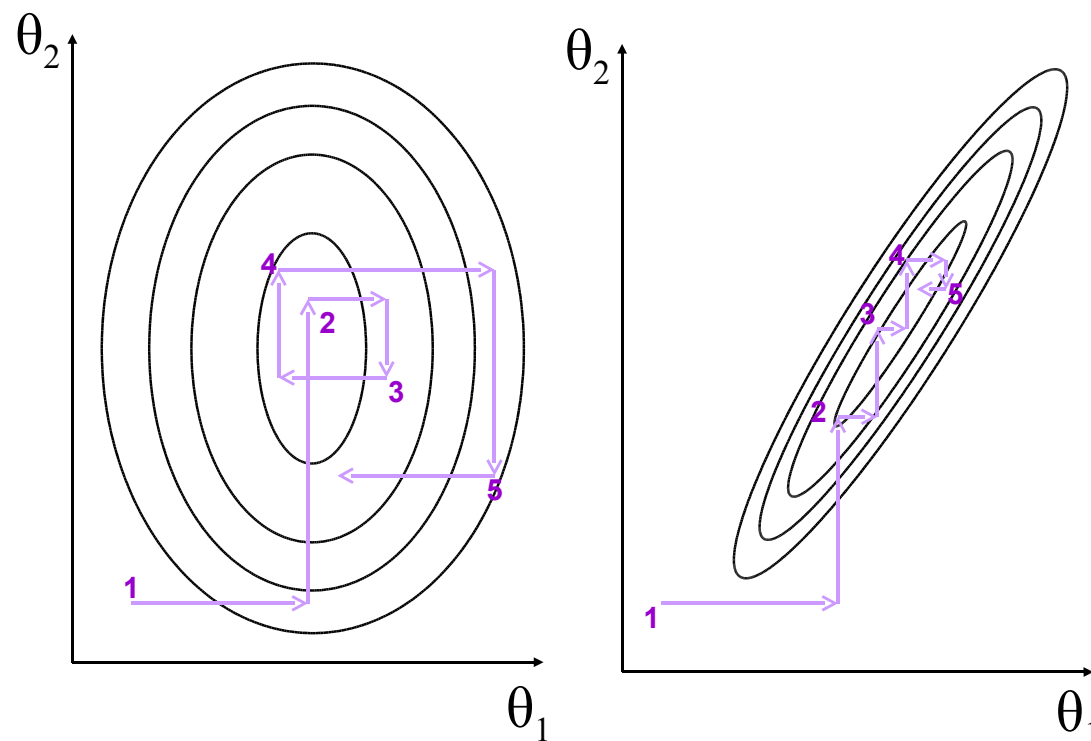


The big idea: with a large sample from a distribution – e.g. the posterior – we can approximate **any** property of that distribution.

Monte Carlo simulation

It may *seem* like sampling would require full knowledge of the posterior, and be at least as much work as the integration.

But this isn't true: one way to do it is the *Gibbs Sampler* – here shown for two examples



Gibbs updates parameters 'one at a time', using only $p(\theta_1|\theta_2)$, then $p(\theta_2|\theta_1)$ – so no hard integration to do. The sequence of samples $\boldsymbol{\theta}^{(s)}$ (a *Markov Chain*) are autocorrelated, i.e. dependent, but the posterior **is** covered appropriately.

Monte Carlo simulation

Recall the posterior can be written as $p(\theta_1, \theta_2 | \mathbf{Y}) = p(\theta_2 | \mathbf{Y}) \times p(\theta_1 | \theta_2, \mathbf{Y})$, so if we can generate from conditional $p(\theta_1 | \theta_2, \mathbf{Y})$ – in one variable – with frequency $p(\theta_2 | \mathbf{Y})$ for each θ_2 , we get a sample from the full posterior.

Gibbs does this, using *just* the conditionals, iterating between these steps:

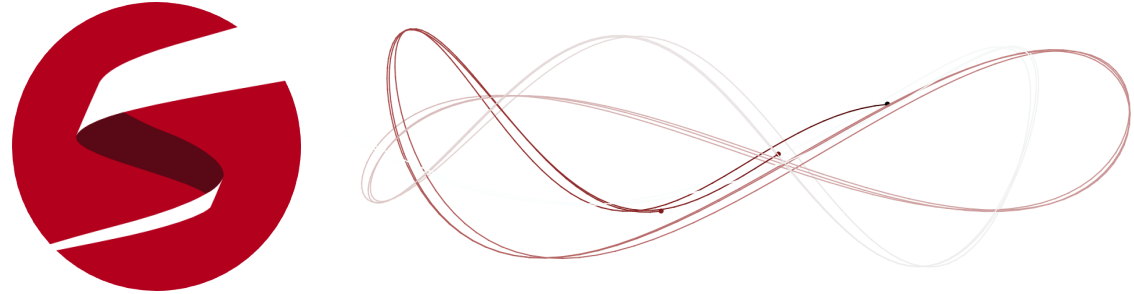
$$\begin{aligned}\theta_1^{(s)} &\sim p(\theta_1 | \theta_2^{(s-1)}, \mathbf{Y}) \\ \theta_2^{(s)} &\sim p(\theta_2 | \theta_1^{(s)}, \mathbf{Y})\end{aligned}$$

to produce a *chain* $(\theta_1^{(0)}, \theta_2^{(0)}), (\theta_1^{(1)}, \theta_2^{(1)}), \dots, (\theta_1^{(s)}, \theta_2^{(s)}), \dots$

- If the chain is long enough ($s \rightarrow \infty$), this sequence *is* a sample from $p(\theta_1, \theta_2 | \mathbf{Y})$, no matter where you started
- For more parameters, update each single θ_k in turn, then start again

MCMC: with Stan

Stan works out all the conditionals for us, and how to update based on them ;



- Specify just a model, including priors, and tell Stan what the data are
- Stan writes code to sample from the posterior, by ‘walking around’ – actually it runs the *No U-Turn Sampler*, a more advanced algorithm for exploring the parameter space
- Stan runs this code, and reports back all the samples
- The `rstan` package lets you run chains from R
- Some modeling limitations – no discrete parameters – but becoming very popular; works well with some models where other software would struggle
- Requires declarations (like C++) – unlike R – so models require a bit more typing...

MCMC: with Stan

For our linear regression, with unknown σ^2 ;

```
cat(file="FT0example.stan", "  
data {  
  int n; //the number of observations  
  int p; //the number of columns in the model matrix  
  real y[n]; //the response  
  matrix[n,p] X; //the model matrix  
  real g; // Zellner scale factor  
  vector[p] mu; // Zellner prior mean (all zeros)  
  matrix[p,p] XtXinv; // information matrix  
}  
parameters {  
  vector[p] beta; //the regression parameters  
  real invsigma2; //the precision, a.k.a. inverse-variance  
}  
transformed parameters {  
  vector[n] linpred;  
  cov_matrix[p] Sigma;
```

MCMC: with Stan

```
real sigma;
linpred = X*beta;
sigma = 1/sqrt(invsigma2);
for (j in 1:p){
  for (k in 1:p){
    Sigma[j,k] = g*sigma^2*XtXinv[j,k];
  } } }
model {
  beta ~ multi_normal(mu, Sigma);
  y ~ normal(linpred, sigma);
  invsigma2 ~ gamma(0.5, 1.839); // we took nu0=1, sigma0=1.91
}
")
# do the MCMC, store the results
library("rstan")
stan2 <- stan(file = "FT0example.stan",
data = list(n=n,p=p, y=y, X=X, g=n, mu=rep(0,p), XtXinv=solve(crossprod(X)) ),
iter = 100000, chains = 1, pars=c("beta","sigma"))
```

MCMC: with Stan

Summarize the posterior by summarizing the MCMC samples:

```
> print(stan2)
Inference for Stan model: FT0example.
1 chains, each with iter=1e+05; warmup=50000; thin=1;
post-warmup draws per chain=50000, total post-warmup draws=50000.
```

	mean	se_mean	sd	2.5%	25%	50%	75%	97.5%	n_eff	Rhat
beta[1]	0.50	0.02	2.47	-4.39	-1.11	0.50	2.10	5.39	13849	1
beta[2]	1.48	0.03	3.50	-5.42	-0.80	1.47	3.78	8.43	13720	1
beta[3]	2.13	0.01	0.75	0.65	1.64	2.13	2.61	3.61	14000	1
beta[4]	2.56	0.01	1.06	0.46	1.87	2.56	3.24	4.65	14015	1
sigma	3.39	0.00	0.55	2.52	3.00	3.32	3.70	4.66	20814	1
lp__	-40.95	0.01	1.64	-45.04	-41.79	-40.61	-39.75	-38.79	16583	1

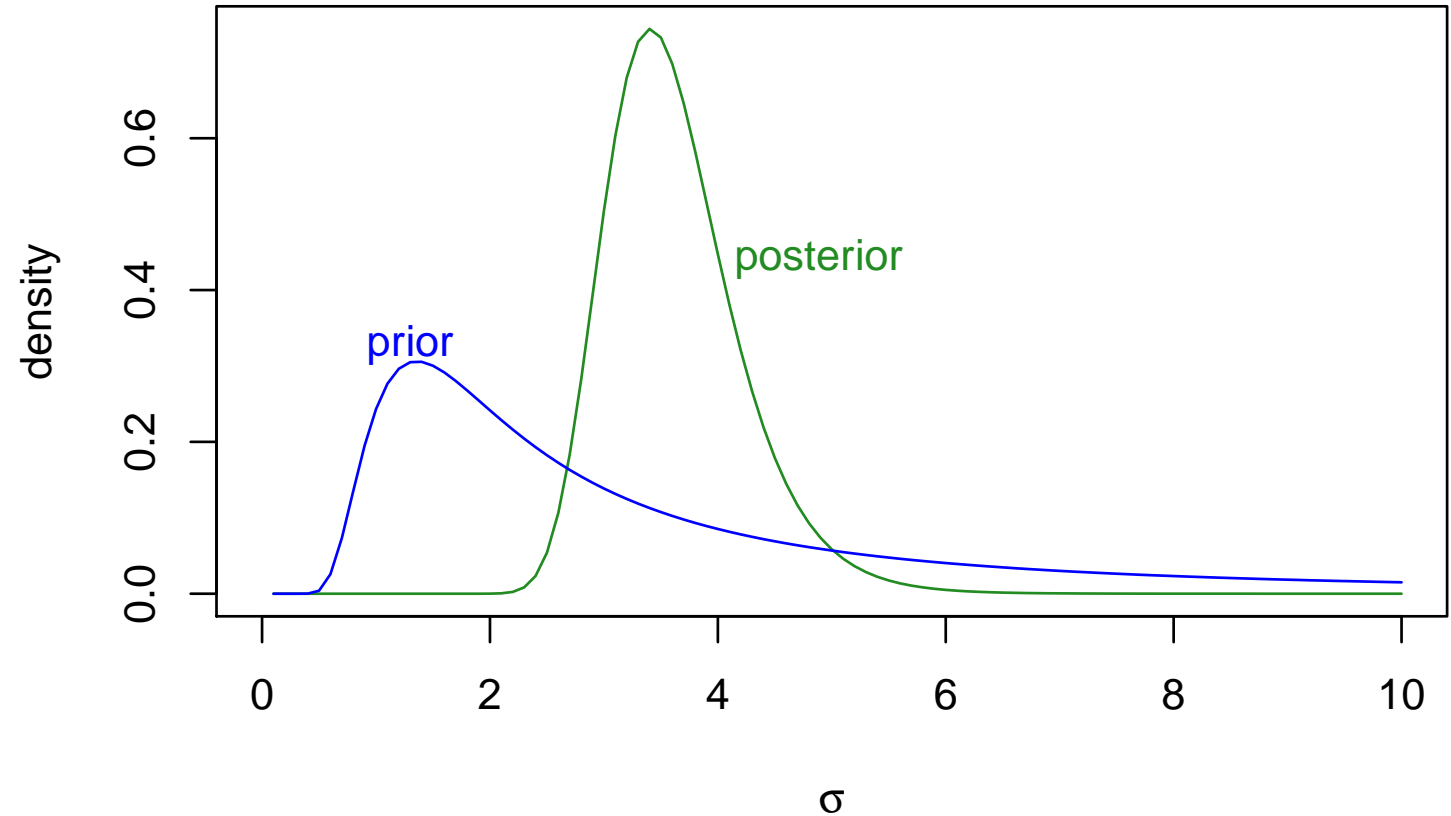
```
> # compare with the non-Bayes version
> round(cbind(summary(lm(y~xg*xa))$coef[,1:2], confint(lm(y~xg*xa))), 2)
```

	Estimate	Std. Error	2.5 %	97.5 %
(Intercept)	0.49	1.06	-1.75	2.73
xg	1.59	1.49	-1.57	4.76
xa	2.24	0.32	1.57	2.92
xg:xa	2.68	0.45	1.72	3.63

MCMC: with Stan

Why are the estimates similar but the intervals so different?

Here are the prior and posterior for σ ;



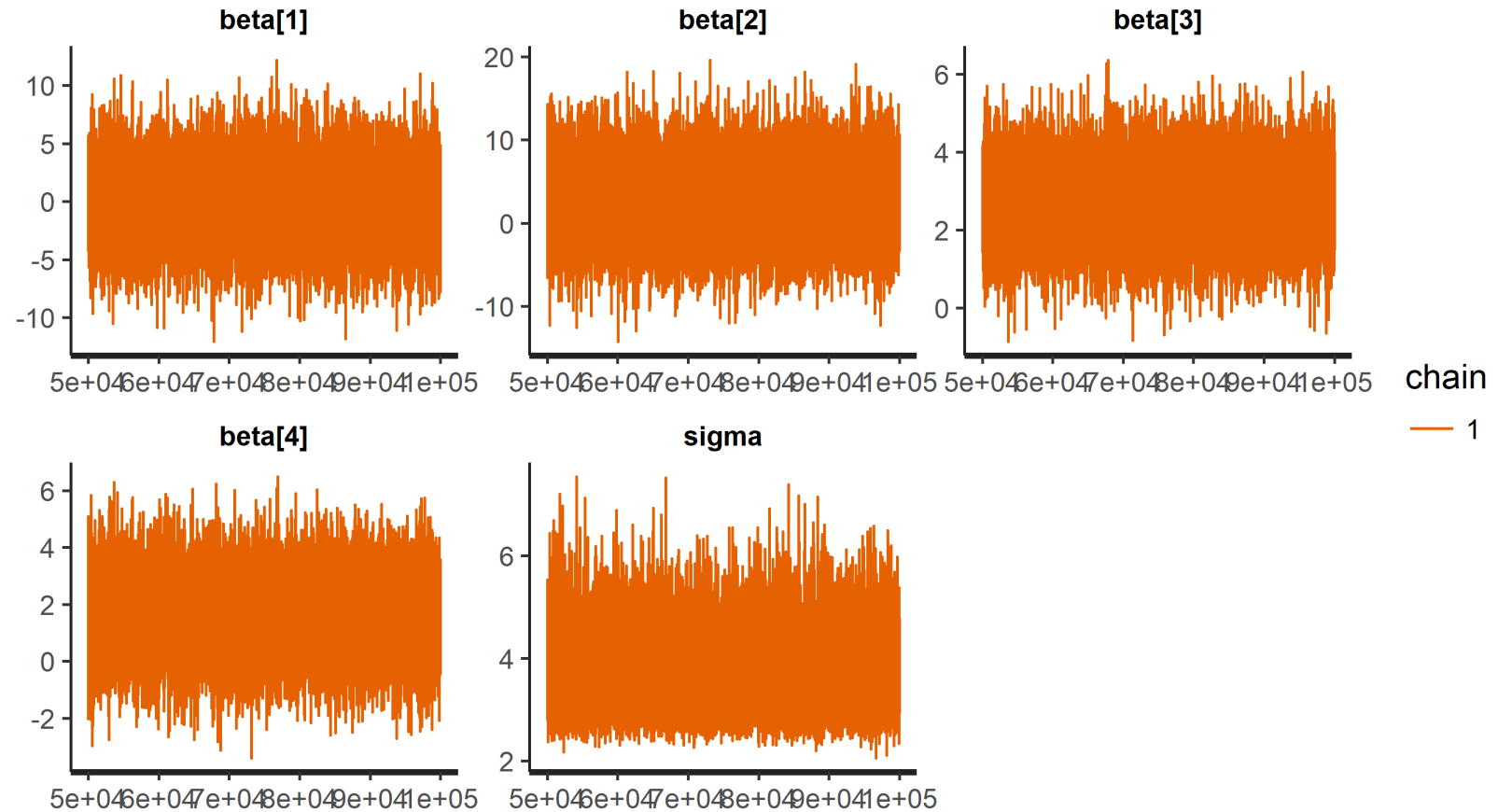
The ‘best guess’ estimate is $\hat{\sigma} = \sigma_0 = 1.91$ – but the prior also supports much larger values – with which the data don’t strongly disagree.

MCMC: with Stan

To see where the
'chain' went...

```
> traceplot(stan2)
```

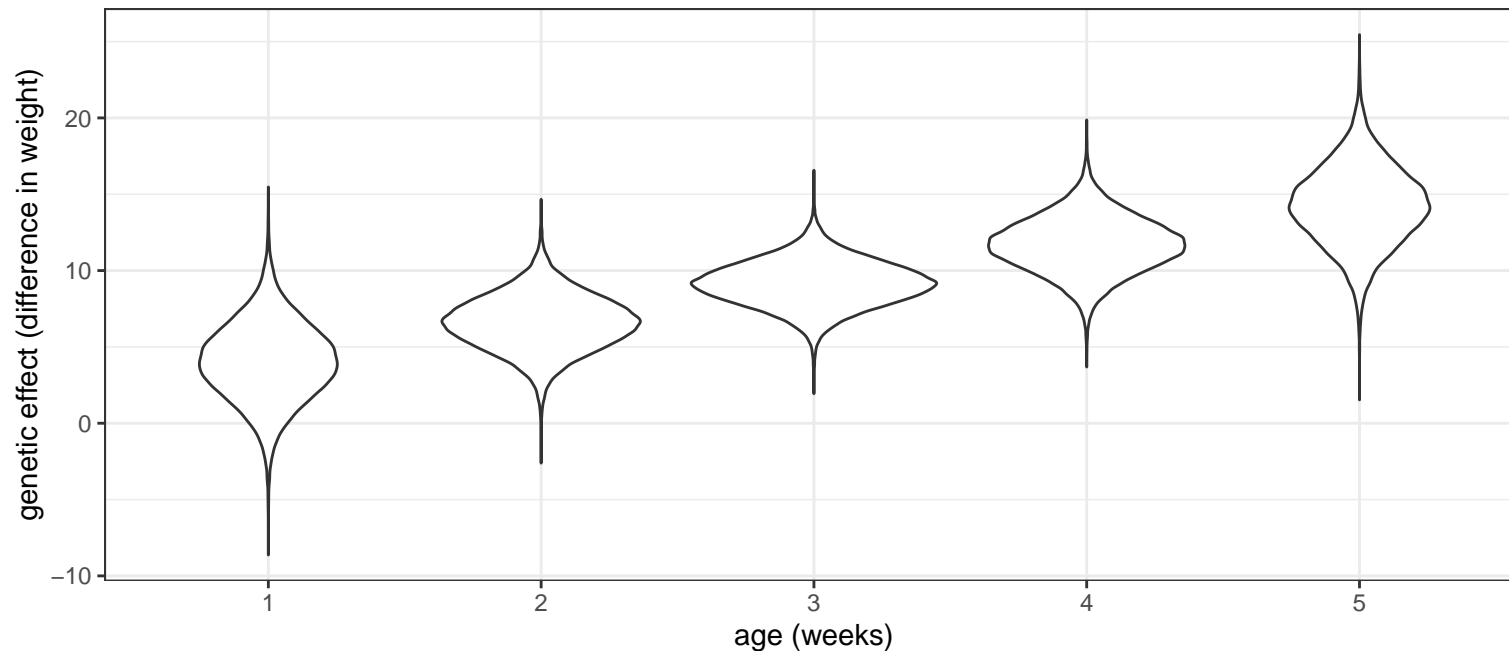
Tip: save these plots as
PNGs not PDFs!



MCMC: with Stan

With the posterior samples in R, we can evaluate the posterior of any function of them. For example, the genetic effect at each of the five ages;

$$\mathbb{E}[Y|\text{age}, +/ -] - \mathbb{E}[Y|\text{age}, -/-] = (\beta_1 + \beta_2) + (\beta_3 + \beta_4) \times \text{age} - (\beta_1 + \beta_3 \times \text{age}) = \beta_2 + \beta_4 \times \text{age}$$



MCMC: summary so far

- Stan - and other similar software - may look like overkill for this 'conjugate' problem, but Stan can provide posteriors for almost any model
- The 'modeling' language is based on R
- Users do have to decide how long a chain to run, and how long to 'burn in' for at the start of the chain. These are not easy to answer! We'll see some diagnostics in later sessions

Summary

- Linear regressions are of great applied interest
- Conjugacy helps us quickly explore how informative the prior is, versus the data
- ...but with MCMC we can fit a huge variety of models
- Inference using MCMC output is also flexible; no restriction on parameters we can learn about

Bonus tracks: what if the model's wrong? (***)

Different types of violation—in decreasing order of how much they typically matter in practice

- Just have the wrong data (!) i.e. not the data you claim to have
- Observations are not independent, e.g. repeated measures on same mouse over time
- Mean model is incorrect
- Error terms do not have constant variance
- Error terms are not Normally distributed

Having the wrong data, where possible, should be addressed before analyses. Here we'll focus on how much post-analysis violations matter.

Wrong model: dependent outcomes

- Observations from the same mouse are more likely to be similar than those from different mice (even if they have same age and genotype)
- SBP from subjects (even with same age, genotype etc) in the same family are more likely to be similar than those in different families – perhaps unmeasured common diet?
- Spatial and temporal relationships also tend to induce correlation

If the pattern of relationship is known, can allow for it – typically in “random effects models” – see later session.

If not, treat results with caution! Precision is likely over-stated.

Wrong model: mean model

Even when the scientific background is highly informative about the variables of interest (e.g. we want to know about the association of Y with x_1 , adjusting for $x_2, x_3...$) there is rarely strong information about the form of the model

- Does mean weight increase with age? age^2 ? age^3 ?
- Could the effect of genotype also change non-linearly with age?

Including quadratic terms is a common approach – but quadratics are sensitive to the tails. Instead, including “spline” representations of covariates allows the model to capture many patterns.

Including interaction terms (as we did with $x_{i,2} \times x_{i,3}$) lets one covariate's effect vary with another.

(Deciding which covariates to use is addressed in the Model Choice session.)

Wrong model: non-constant variance

This is plausible in many situations; perhaps e.g. young mice are harder to measure, i.e. more variables. Or perhaps the FTO variant affects weight regulation — again, more variance.

- Having different variances at different covariate values is known as *heteroskedasticity*
- Unaddressed, it can result in over- or under-statement of precision

The most obvious approach is to model the variance, i.e.

$$\begin{aligned} Y_i &= \beta^T x_i + \epsilon_i, \\ \epsilon_i &\sim \text{Normal}(0, \sigma_i^2), \end{aligned}$$

where σ_i depends on covariates, e.g. σ_{homozy} and $\sigma_{heterozy}$ for the two genotypes.

Of course, these parameters need priors. Constraining variances to be positive also makes choosing a model difficult in practice.

Robust standard errors (in Bayes)

In linear regression, some robustness to model-misspecification and/or non-constant variance is available – but it relies on interest in linear ‘trends’. Formally, we can define parameter

$$\boldsymbol{\theta} = \operatorname{argmin} \mathbb{E}_x \left[\left(\mathbb{E}_y[y|x] - \mathbf{X}^t \boldsymbol{\theta} \right)^2 \right],$$

i.e. the straight line that best-captures random-sampling, in a least-squares sense.

- This ‘trend’ can capture important features in how the mean y varies at different x
- Fitting extremely flexible Bayesian models, we get a posterior for $\boldsymbol{\theta}$
- The posterior mean approaches $\hat{\boldsymbol{\beta}}_{\text{OLS}}$, in large samples
- The posterior variance approaches the ‘robust’ *sandwich estimate*, in large samples (details in [Szpiro et al, 2011](#))

Robust standard errors (in Bayes)

The OLS estimator can be written as $\hat{\beta}_{\text{ols}} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{y} = \sum_{i=1}^n c_i y_i$, for appropriate c_i .

True variance	$\text{Var}[\hat{\beta}]$	$=$	$\sum_{i=1}^n c_i^2 \text{Var}[Y_i]$
Robust estimate	$\widehat{\text{Var}}_R[\hat{\beta}]$	$=$	$\sum_{i=1}^n c_i^2 e_i^2$
Model-based estimate	$\widehat{\text{Var}}_M[\hat{\beta}]$	$=$	$\text{Mean}(e_i^2) \sum_{i=1}^n c_i^2$

where $e_i = y_i - \mathbf{x}_i^T \hat{\beta}_{\text{ols}}$, the residuals from fitting a linear model.

Non-Bayesian sandwich estimates are available through R's `sandwich` package – much quicker than Bayes with a very-flexible model. For correlated outcomes, see the `GEE` package for generalizations.

Wrong model: Non-Normality

This is not a big problem for learning about population parameters;

- The variance statements/estimates we just saw don't rely on Normality
- The *central limit theorem* means that $\hat{\beta}$ ends up Normal anyway, in large samples
- In small samples, expect to have limited power to detect non-Normality
- ... except, perhaps, for extreme outliers (data errors?)

For prediction – where we assume that outcomes do follow a Normal distribution – this assumption is more important.