

2017 SISG Module 13: Bayesian Statistics for Genetics

Lecture 5: Multinomial Sampling

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Outline

Introduction and Motivating Examples

Bayesian Analysis of Multinomial Data

Derivation of the Posterior and Prior Specification

Inference for Parameters of Interest

Analysis of HWE Data

Appendix: BF Detail

Introduction

- In this lecture we will consider the Bayesian modeling of multinomial data.
- The examination of **Hardy-Weinberg equilibrium** will be used to motivate the multinomial model.
- Again, **conjugate priors** will be used, though sampling from the posterior will be emphasized as a method for flexible inference.
- **Bayes factors** will be used as a measure of evidence for hypothesis testing.

Motivating Example: Testing for HWE

- For simplicity we consider a diallelic marker, and suppose we obtain a random sample of genotypes for n individuals.
- The form of the data is

	Genotype			Total
	A_1A_1	A_1A_2	A_2A_2	
Count	n_1	n_2	n_3	n
Population Frequency	q_1	q_2	q_3	1

- So the model contains 3 probabilities (which sum to 1) q_1, q_2, q_3 ; hence, there are 2 **free** parameters.
- Suppose the proportions of alleles A_1 and A_2 in a given generation are p_1 and $p_2 = 1 - p_1$.
- In terms of q_1, q_2, q_3 :

$$p_1 = q_1 + \frac{q_2}{2}$$

$$p_2 = \frac{q_2}{2} + q_3$$

Motivating Example: Testing for HWE

- HWE is the **statistical independence** of an individual's alleles at a locus.
- Under HWE, the probability distribution for the genotype of an individual in the next generation is:

	Genotype			
	A_1A_1	A_1A_2	A_2A_2	
Proportion	p_1^2	$2p_1p_2$	p_2^2	1

- Reasons for **deviation** from HWE include: small population size, selection, inbreeding and population structure.

A Toy Example

Example:

- Consider the data $n_1 = 88$, $n_2 = 10$, $n_3 = 2$.
- Are these frequencies consistent with HWE?
- The MLEs are:

$$\begin{aligned}\hat{q}_1 &= 0.88 & \hat{q}_2 &= 0.10 & \hat{q}_3 &= 0.02 \\ \hat{p}_1 &= 0.93 & \hat{p}_2 &= 0.07\end{aligned}$$

- For these data the exact p -value for

$$H_0 : q_1 = p_1^2, \quad q_2 = 2p_1p_2, \quad q_3 = p_2^2$$

is 0.0654.

Critique of Non-Bayesian Approach

- Testing for HWE is carried out via (**asymptotic**, i.e., large sample) χ^2 tests or **exact** tests.
- χ^2 tests require very large sample sizes for accurate p -values.
- The exact test can be **computationally expensive** to perform, when there are many alleles/samples.
- Under the null of HWE, the **discreteness** of the test statistic causes difficulties.
- In general, how to decide on a **significance level**? The level should be a function of sample size (and in particular should decrease as sample size increases), but how should it be chosen?
- Estimation depends on **asymptotic approximations** (i.e., large sample sizes).
- Estimation also difficult due to **awkward constraints** on parameters (particularly with many alleles).

Elements of Bayes Theorem: The Likelihood

- We assume n independent draws with common probabilities $\mathbf{q} = (q_1, q_2, q_3)$.
- In this case, the distribution of n_1, n_2, n_3 is **multinomial**:

$$\Pr(n_1, n_2, n_3 | q_1, q_2, q_3) = \frac{n!}{n_1! n_2! n_3!} q_1^{n_1} q_2^{n_2} q_3^{n_3}. \quad (1)$$

- For fixed \mathbf{n} , we may view (1) as a function of \mathbf{q} – this is the **likelihood function**.
- The **maximum likelihood estimate** (MLE) is

$$\hat{\mathbf{q}} = \left(\frac{n_1}{n}, \frac{n_2}{n}, \frac{n_3}{n} \right).$$

- The MLE gives the highest probability to the observed data, i.e. maximizes the likelihood function.

The Dirichlet Distribution as a Prior Choice for a Multinomial \mathbf{q}

- Once the likelihood is specified we need to think about the **prior** distribution.
- We require a prior distribution over (q_1, q_2, q_3) — not straightforward since the three probabilities all lie in $[0,1]$, and must sum to 1.
- A distribution that satisfies these requirements is the **dirichlet** distribution, denoted **dirichlet** (v_1, v_2, v_3) and has density:

$$p(q_1, q_2, q_3) = \frac{\Gamma(v_1 + v_2 + v_3)}{\Gamma(v_1)\Gamma(v_2)\Gamma(v_3)} \times q_1^{v_1-1} q_2^{v_2-1} q_3^{v_3-1}$$

$$\propto q_1^{v_1-1} q_2^{v_2-1} q_3^{v_3-1}$$

where $\Gamma(\cdot)$ denotes the gamma function.

The Dirichlet Distribution as a Prior Choice for a Multinomial \mathbf{q}

- The **dirichlet**(v_1, v_2, v_3) prior:

$$p(q_1, q_2, q_3) = \frac{\Gamma(v_1 + v_2 + v_3)}{\Gamma(v_1)\Gamma(v_2)\Gamma(v_3)} \times q_1^{v_1-1} q_2^{v_2-1} q_3^{v_3-1}$$

$$\propto q_1^{v_1-1} q_2^{v_2-1} q_3^{v_3-1}.$$

- $v_1, v_2, v_3 > 0$ are specified to reflect prior beliefs about (q_1, q_2, q_3) .
- The dirichlet distribution can be used with general multinomial distributions (i.e. for $k = 2, 3, \dots$ categories).
- The beta distribution is a special case of the dirichlet when there are two categories only.

Dirichlet Prior

- The **mean** and **variance** are

$$E[q_i] = \frac{v_i}{v_1 + v_2 + v_3} = \frac{v_i}{v}$$

$$\text{var}(q_i) = \frac{E[q_i](1 - E[q_i])}{v_1 + v_2 + v_3 + 1} = \frac{E[q_i](1 - E[q_i])}{v + 1}$$

for $i = 1, 2, 3$, where $v = v_1 + v_2 + v_3$.

- Large values of v increase the influence of the prior.
- The dirichlet has a single parameter only (v) to control the **spread** for all of the dimensions, which is a deficiency.
- The quartiles may be empirically calculated from samples.

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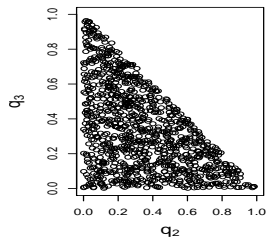
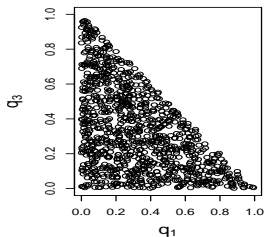
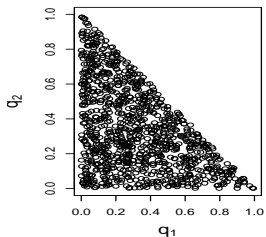
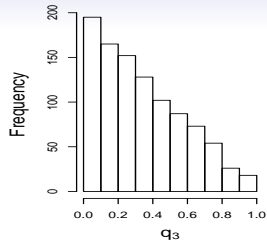
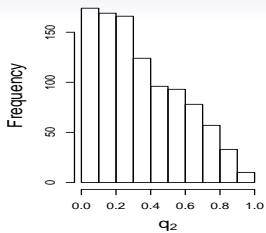
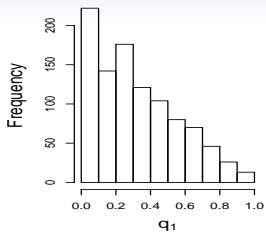


Figure 1: Samples from a $\text{dirichlet}(1, 1, 1)$ distribution. The mean is $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$.

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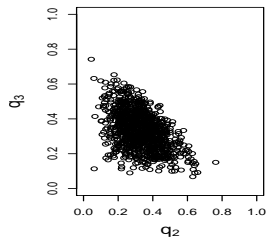
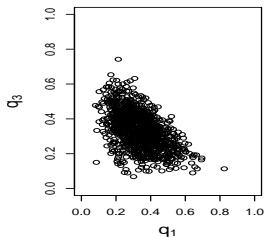
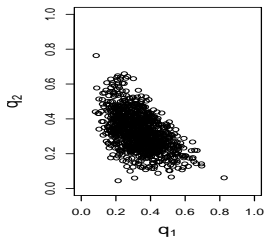
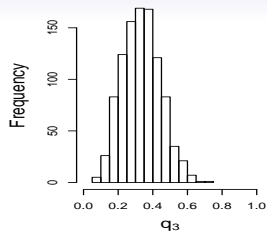
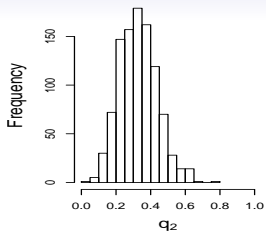
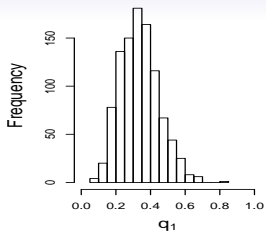


Figure 2: Samples from a $\text{dirichlet}(6, 6, 6)$ distribution. The mean is $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$.

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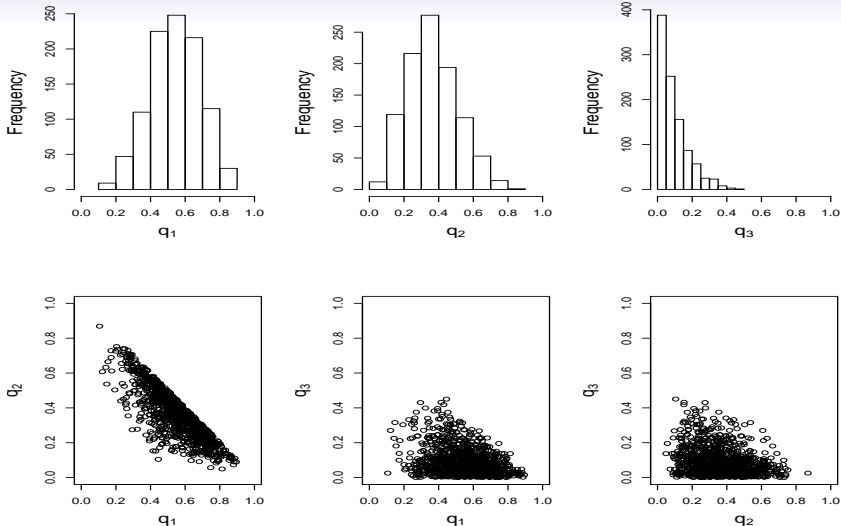


Figure 3: Samples from a $\text{dirichlet}(6, 4, 1)$ distribution. The mean is $\left(\frac{6}{11}, \frac{4}{11}, \frac{1}{11}\right) = (0.55, 0.36, 0.09)$.

Posterior Distribution

- Combining the Dirichlet prior, $\text{dirichlet}(v_1, v_2, v_3)$, with the multinomial likelihood gives the posterior:

$$\begin{aligned} p(q_1, q_2, q_3 | \mathbf{n}) &\propto \text{Pr}(\mathbf{n} | \mathbf{q}) \times p(\mathbf{q}) \\ &\propto q_1^{n_1} q_2^{n_2} q_3^{n_3} \times q_1^{v_1-1} q_2^{v_2-1} q_3^{v_3-1} \\ &= q_1^{n_1+v_1-1} q_2^{n_2+v_2-1} q_3^{n_3+v_3-1}. \end{aligned}$$

- This distribution is another Dirichlet:

$$\text{dirichlet}(n_1 + v_1, n_2 + v_2, n_3 + v_3).$$

- Notice: “as if” we had observed counts $(n_1 + v_1, n_2 + v_2, n_3 + v_3)$.

Choosing a Prior

- The **posterior mean** for the expected proportion of counts in cell i is, for $i = 1, 2, 3$:

$$\begin{aligned} E[q_i|\mathbf{n}] &= \frac{n_i + v_i}{n + v} \\ &= \frac{n_i}{n} \frac{n}{n + v} + \frac{v_i}{v} \frac{v}{n + v} \\ &= \text{MLE} \times W + \text{Prior Mean} \times (1 - W) \end{aligned}$$

where $n = n_1 + n_2 + n_3$, $v = v_1 + v_2 + v_3$.

- The **weight** W is

$$W = \frac{n}{n + v}$$

which is the proportion of the **total information** ($n + v$) that is contributed by the data (n).

Choosing a Prior

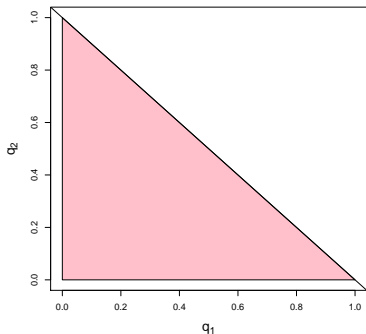
- Recall the prior mean is

$$\left(\frac{v_1}{v}, \frac{v_2}{v}, \frac{v_3}{v} \right)$$

- These forms help to choose v_1, v_2, v_3 .
- As with the beta distribution we may specify the prior means, and the relative weight that the prior and data contribute: n and v are on a comparable scale.
- For example, suppose we believe that event 1 is four times as likely as each of event 2 or event 3.
- Then we may specify the means in the ratios 4:1:1.
- Suppose $n = 24$ and we wish to allow the prior contribution to be a half of this total (and therefore a third of the complete information). Then the **prior sample size** is $v = 12$ and the prior mean requirement gives

$$v_1 = 8, v_2 = 2, v_3 = 2.$$

A Uniform Prior



An obvious choice of parameters is $v_1 = v_2 = v_3 = 1$ to give a prior that is uniform over the simplex:

$$\pi(q_1, q_2, q_3) = 2$$

for

$$0 < q_1, q_2, q_3 < 1, \quad q_1 + q_2 + q_3 = 1$$

Note: not uniform over all parameter of interests, as we see shortly

Simple HWE Example

- The data is

$$n_1 = 88, n_2 = 10, n_3 = 2.$$

- We assume a flat dirichlet prior on the allowable values of \mathbf{q} :

$$v_1 = v_2 = v_3 = 1.$$

- This gives the posterior as **dirichlet(88 + 1, 10 + 1, 2 + 1)** with posterior means:

$$\begin{aligned} E[q_1 | \mathbf{n}] &= \frac{1 + 88}{3 + 100} = \frac{89}{103} \\ E[q_2 | \mathbf{n}] &= \frac{1 + 10}{3 + 100} = \frac{11}{103} \\ E[q_3 | \mathbf{n}] &= \frac{1 + 2}{3 + 100} = \frac{3}{103}. \end{aligned}$$

- Note the similarity to the MLEs of

$$\left(\frac{88}{100}, \frac{10}{100}, \frac{2}{100} \right).$$

Simple HWE Example

- We continue with this example and now examine posterior distributions.
- We generate samples from

$\text{dirichlet}(88 + 1, 10 + 1, 2 + 1)$.

- As posterior summaries we display, in Figure 4:
 - Histograms of the 3 univariate marginal distributions $p(q_1|\mathbf{y})$, $p(q_2|\mathbf{y})$, $p(q_3|\mathbf{y})$.
 - Scatterplots of the 3 bivariate marginal distributions $p(q_1, q_2|\mathbf{y})$, $p(q_1, q_3|\mathbf{y})$, $p(q_2, q_3|\mathbf{y})$.
- On each plot we indicate the MLEs for the general model, i.e. the non-HWE model (in red) and under the assumption of HWE (in blue).

Samples from the Posterior

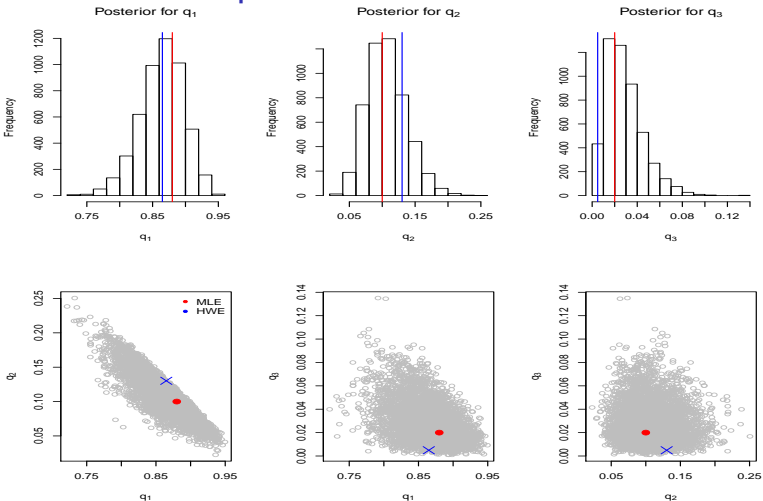


Figure 4: Univariate and bivariate posterior distributions for $\mathbf{n} = (88, 10, 2)$. MLEs in red for the general model and in blue for the HWE model.

Bayes analysis of (88,10,2) data

- As expected with a sample size of $n = 100$ and a flat prior, the MLEs lie close to the center of the posteriors.
- Note the asymmetry of the posteriors.
- Asymptotic confidence intervals of the form $\hat{q}_i \pm 1.96 \times \text{se}(\hat{q}_i)$ would be symmetric.

Bayes analysis of (88,10,2) data

- In the context of a binomial sampling model and interest in a particular point (for example, $\theta = 0.5$) we could examine intervals for θ .
- In a multinomial context the situation is more complex; shortly we will examine **Bayes factors** to carry out hypothesis testing.

Parameters of Interest

	Genotype			Total
	A_1A_1	A_1A_2	A_2A_2	
Population Frequency	q_1	q_2	q_3	1

- Rather than q_1, q_2, q_3 , we may be interested in other parameters of interest.
- In the HWE context: Let X_1 and X_2 be 0/1 indicators of A_1 for the two alleles at a locus.
- The covariance between X_1 and X_2 is the **disequilibrium coefficient**:

$$D = q_1 - p_1^2$$

Under HWE $q_1 = p_1^2$, and the covariance is zero.

- Another quantity of interest (Shoemaker *et al.*, 1998) is

$$\psi = \frac{q_2^2}{q_1 q_3}.$$

Under HWE, $\psi = 4$.

Parameters of Interest

- The **inbreeding coefficient** is

$$f = \frac{q_1 - p_1^2}{p_1 p_2}$$

- The variance of X_1 and X_2 is $p_1(1 - p_1) = p_1 p_2$ and so f is the correlation.
- We may express q_1, q_2, q_3 as

$$q_1 = p_1^2 + p_1(1 - p_1)f$$

$$q_2 = 2p_1(1 - p_1)(1 - f)$$

$$q_3 = (1 - p_1)^2 + p_1(1 - p_1)f$$

- Positive** values of f indicate an excess of homozygotes (and may indicate inbreeding), while **negative** values indicate an excess of heterozygotes.

Parameters of Interest

- Each of D , ψ and f are complex functions of q_1, q_2, q_3 and given a Dirichlet prior for the latter do not have known posterior forms.
- The “flat” prior for \mathbf{q} , $\text{dirichlet}(1, 1, 1)$, does not correspond to a flat prior for D, f, ψ , as Figure 5 shows.

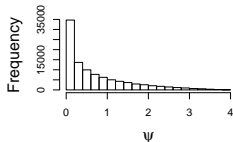
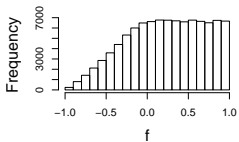
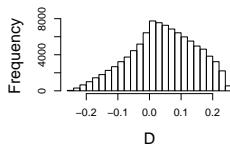
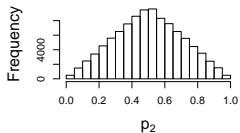
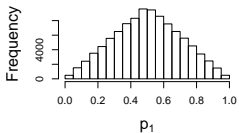
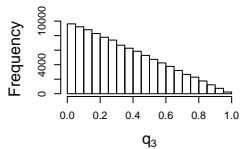
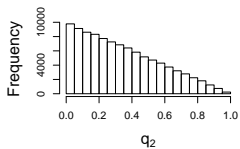
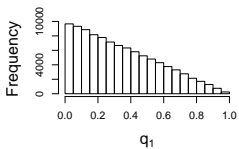
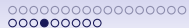


Figure 5: Samples from a $\text{dirichlet}(1,1,1)$ for various functions.

Implied Prior on Functions of Interest

- **Very important point:** As we saw in the binomial development, you can't be "flat" on every scale, but the implications of particular priors can be assessed via simulation.
- We emphasize that we are not uniform on the marginal distributions for q_i , since these follow

$$\text{beta}(v_i, v - v_i)$$

distributions, i.e. $\text{beta}(1,2)$ if $v_1 = v_2 = v_3 = 1$.

- The priors on the measures of distance from HWE are far from uniform.
- For example, with a "flat" Dirichlet prior $\text{dirichlet}(1,1,1)$ the prior probability that $f > 0$ is 0.67.

Bayesian Approaches to HWE

Previous Bayesian approaches include:

- Altham (1971).
- Pereira and Rogatko (1984).
- Lindley (1988).
- Shoemaker *et al.* (1998).
- Montoya-Delgado *et al.* (2001).
- Consonni *et al.* (2008).
- Wakefield (2010).
- Consonni *et al.* (2011).
- Puig *et al.* (2017).

Bayes factors for HWE

- Recall that Bayes factors measure the evidence in a sample for one hypothesis, as compared to an alternative.
- We derive the Bayes factor for multinomial data in the context of testing for HWE.
- We wish to test

H_0 : HWE versus H_1 : Not HWE.

- We need to specify priors on the null and alternatives, and then calculate the **Bayes factor**:

$$\frac{\Pr(\mathbf{n}|H_0)}{\Pr(\mathbf{n}|H_1)}$$

where p_1 and (q_1, q_2) are the parameters under the null and alternative, respectively.

The HWE Bayes Factor

- The **Bayes factor**, measuring the evidence in the data for the null, as compared to the alternative is:

$$\text{BF} = \frac{2^{n_2} \Gamma(w) \Gamma(2n_1 + n_2 + w_1) \Gamma(v_1) \Gamma(v_2) \Gamma(v_3) \Gamma(n_2 + 2n_3 + w_2) \Gamma(n + v)}{\Gamma(w_1) \Gamma(w_2) \Gamma(2n + w) \Gamma(v) \Gamma(n_1 + v_1) \Gamma(n_2 + v_2) \Gamma(n_3 + v_3)}.$$

- This appears complex, but is just a function of the **observed data**, and the **prior inputs**, and can be easily evaluated¹.
- If $\text{BF} > 1$ (< 1) the data are **more** (**less**) likely to have come from the null.
- Can be readily extended to $k > 2$ alleles.
- We next consider a formal decision rule.

¹When we work out a χ^2 tail area we don't worry about the form of the distribution we just use the relevant function in our favorite software

Bayesian Decision Theory

- Decision as to reject H_0 in favor of H_1 depends on the **costs** of making the two types of error:

		Decision	
		Report H_0	Report H_1
Truth	H_0	0	C_I
	H_1	C_{II}	0

- Costs of making the two types of error C_I is the cost of a type I error and C_{II} the cost of a type II error.
- The decision theory solution is to **report H_1** if:

$$\text{Posterior Odds of } H_0 = \text{BF} \times \text{Prior Odds} < \frac{C_{II}}{C_I} = R$$

so that we only need to consider the ratio of costs R .

- If $\frac{C_{II}}{C_I} = 4$ (type II errors four times as bad as type I errors) then report H_1 if

$$\text{Posterior Odds of } H_0 < 4,$$

i.e. if

$$\Pr(H_1 | \text{data}) > 0.2.$$

A Simple Example

We again consider the data $n_1 = 88, n_2 = 10, n_3 = 2$.

These data give a *p-value* of 0.0654.

With “flat” conjugate Dirichlet priors ($w_1 = w_2 = v_1 = v_2 = v_3 = 1$) we obtain a **Bayes factor** of 1.54 so that the data are 50% more likely under the null than the alternative, so the evidence in favor of H_0 is not strong.

With a prior probability of the null π_0 , to give a prior odds of $\pi_0/(1 - \pi_0)$, we have

$$\text{Posterior Odds of } H_0 = \text{BF} \times \frac{\pi_0}{1 - \pi_0}$$

Hence, with $\pi_0 = 0.5$ the posterior odds equal the Bayes factor, i.e. 1.54.

A Simple Example

The posterior probability of the null is

$$\frac{1.54}{1 + 1.54} = 0.61.$$

This probability is very sensitive to the prior on the null.

For example, with $\pi_0 = 2/3$ we obtain a posterior odds of $1.54 \times 2 = 3.08$ to give a posterior probability on the null of

$$\frac{3.08}{1 + 3.08} = 0.75.$$

Posterior Inference for Functions of Interest

Figure 6 shows functions of interest for the $(88, 10, 2)$ example.

Note that the asymptotic confidence interval for f is $(-0.1032, 0.5632)$.

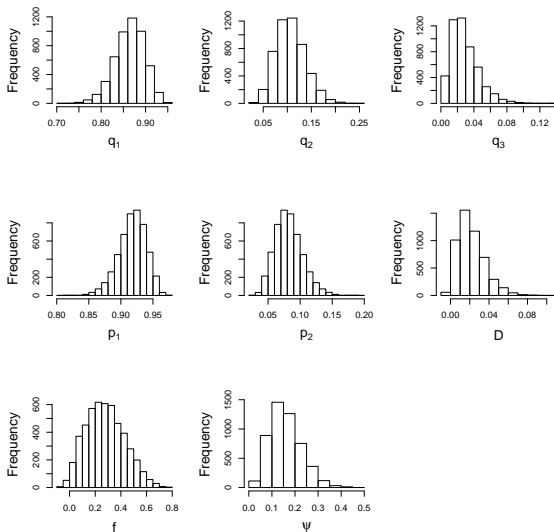
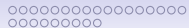


Figure 6: Posterior inference for simple HWE example.

The HWEBayes Package

- The R package **HWEBayes** implements the rejection algorithm and importance sampling (a numerical integration technique), for **testing and estimation** in the HWE context:

<http://cran.r-project.org/web/packages/HWEBayes/index.html>

- The *vignette* contains a worked example.
- Code for a four-allele example is here:

<http://faculty.washington.edu/jonno/HWEBayesFourAllele.R>

- More details of the methodology: Wakefield (2010).

Conclusions

- The dirichlet distribution is convenient but quite inflexible as a prior distribution.
- Alternative priors are more difficult to specify since they are on scales that are more difficult to interpret (e.g. the logistic-normal distribution).
- Bayes factors are **sensitive** to the prior.
- **Monte Carlo sampling** is a powerful tool for inference.
- For **multiple alleles** computation is slow whether the approach is frequentist or Bayesian.

Derivation of Bayes Factor for Assessing HWE

- We need to specify priors on the null and alternatives, and then calculate the **Bayes factor**:

$$\frac{\Pr(\mathbf{n}|H_0)}{\Pr(\mathbf{n}|H_1)} = \frac{\int \Pr(\mathbf{n}|p_1)p(p_1)dp_1}{\int \Pr(\mathbf{n}|q_1, q_2)p(q_1, q_2)dq_1 dq_2}$$

where p_1 and (q_1, q_2) are the parameters under the null and alternative, respectively.

- Under the null we have a single parameter, and under the alternative two.
- Important point:** When Bayes factors are evaluated we need to include the normalizing constants.

HWE Bayes Factor

- Under H_0 and H_1 we must take care to evaluate the probability of the same data, n_1, n_2, n_3 .
- Under the **null**,

$$\Pr(\mathbf{n}|\rho_1) = \Pr(n_1, n_2, n_3|\rho_1) = \frac{n!2^{n_1}}{n_2!n_{12}!n_3!} \rho_1^{2n_1+n_2} (1 - \rho_1)^{n_2+2n_3}.$$

- With a $\text{Be}(w_1, w_2)$ prior on ρ_1 :

$$\begin{aligned} \Pr(n_1, n_2, n_3|H_0) &= \int \Pr(\mathbf{n}|\rho_1) \times p(\rho_1) d\rho_1 \\ &= \frac{n!2^{n_2}\Gamma(w)\Gamma(2n_1 + n_2 + w_1)\Gamma(n_2 + 2n_3 + w_2)}{n_1!n_2!n_3!\Gamma(w_1)\Gamma(w_2)\Gamma(2n + w)} \end{aligned} \quad (2)$$

- This is the probability of the observed data under the null.

HWE Bayes Factor

- The Bayes factor is

$$\frac{\Pr(\mathbf{n}|H_0)}{\Pr(\mathbf{n}|H_1)}$$

and we have just given the form of the numerator.

- We now turn to the denominator.
- Under the **alternative** we assume $\mathbf{q} \sim \text{dirichlet}(v_1, v_2, v_3)$.
- The probability of the data under the alternative is:

$$\begin{aligned} \Pr(n_1, n_2, n_3|H_1) &= \int \Pr(\mathbf{n}|\mathbf{q}_1, \mathbf{q}_2) \times p(\mathbf{q}_1, \mathbf{q}_2) d\mathbf{q}_1 d\mathbf{q}_2 \\ &= \frac{n! \Gamma(v) \Gamma(n_1 + v_1) \Gamma(n_2 + v_2) \Gamma(n_3 + v_3)}{n_1! n_2! n_3! \Gamma(v_1) \Gamma(v_2) \Gamma(v_3) \Gamma(n + v)}. \end{aligned} \quad (3)$$

- Again, just a probability distribution, which we may evaluate for any realization of (n_1, n_2, n_3) .

The HWE Bayes Factor

- Hence, the **Bayes factor**, measuring the evidence in the data for the null, as compared to the alternative is:

$$\begin{aligned} \text{BF} &= \frac{\Pr(n_1, n_2, n_3 | H_0)}{\Pr(n_1, n_2, n_3 | H_1)} \\ &= \frac{2^{n_2} \Gamma(w) \Gamma(2n_1 + n_2 + w_1) \Gamma(v_1) \Gamma(v_2) \Gamma(v_3) \Gamma(n_2 + 2n_3 + w_2) \Gamma(n + v)}{\Gamma(w_1) \Gamma(w_2) \Gamma(2n + w) \Gamma(v) \Gamma(n_1 + v_1) \Gamma(n_2 + v_2) \Gamma(n_3 + v_3)} \end{aligned}$$

which is (2) divided by (3).

- This appears complex, but is just a function of the **observed data**, and the **prior inputs**, and can be easily evaluated.
- If $\text{BF} > 1$ (< 1) the data are **more** (**less**) likely to have come from the null.
- Can be readily extended to $k > 2$ alleles.

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