# 2014 SISG Module 4: Bayesian Statistics for Genetics
# Lecture 4: Multinomial Sampling

Jon Wakefield

Departments of Statistics and Biostatistics
University of Washington



## Outline

## 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 $q_1, q_2, q_3$:

$$\begin{aligned} p_1 &= q_1 + \frac{q_2}{2} \\ p_2 &= \frac{q_2}{2} + q_3 \end{aligned}$$

## 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 $n_{11} = 88, n_{12} = 10, n_{22} = 2$.
- Are these frequencies consistent with HWE?
- The MLEs are:

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

- 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.

```
> library(hwde)
> n1 <- 88
> n2 <- 10
> n3 <- 2
> exact <- hwexact(n1,n2,n3)
> exact
[1] 0.06544
```

## Critique of Non-Bayesian Approach

- Testing for HWE is carried out via (asymptotic, i.e., large sample) $\chi^2$ tests or exact tests.
- $\chi^2$ 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).



## Bayes Theorem

| | 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 |

- The multinomial with three counts is known as the trinomial distribution.
- We have three parameters, $q_1, q_2, q_3$, but they sum to 1, so that effectively we have two parameters.
- We write $\mathbf{q} = (q_1, q_2, q_3)$ to represent the vector of probabilities, and $\mathbf{n} = (n_1, n_2, n_3)$ for the data vector.
- Via Bayes Theorem:

$$p(\mathbf{q}|\mathbf{n}) = \frac{\Pr(\mathbf{n}|\mathbf{q}) \times p(\mathbf{q})}{\Pr(\mathbf{n})}$$

$$\text{Posterior} \propto \text{Likelihood} \times \text{Prior}$$

## 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

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

- 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:

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

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

## The Dirichlet Distribution as a Prior Choice for a Multinomial **q**

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

$$\begin{aligned} p(q_1, q_2, q_3) &= \frac{\Gamma(v_1 + v_2 + v_3)}{\Gamma(v_1)\Gamma(v_2)\Gamma(v_3)} \times q_1^{v_1 - 1} q_2^{v_2 - 1} q_3^{v_3 - 1} \\ &\propto q_1^{v_1 - 1} q_2^{v_2 - 1} q_3^{v_3 - 1}. \end{aligned}$$

- $v_1, v_2, v_3 > 0$ 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 $k = 2, 3, \ldots$ categories).
- The beta distribution is a special case of the dirichlet when there are two categories only.



## Dirichlet Prior

- The mean and variance are

$$\begin{aligned} \mathrm{E}[q_i] &= \frac{v_i}{v} \\ \mathrm{var}(q_i) &= \frac{\mathrm{E}[q_i](1 - \mathrm{E}[q_i])}{v + 1} \end{aligned}$$

  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.

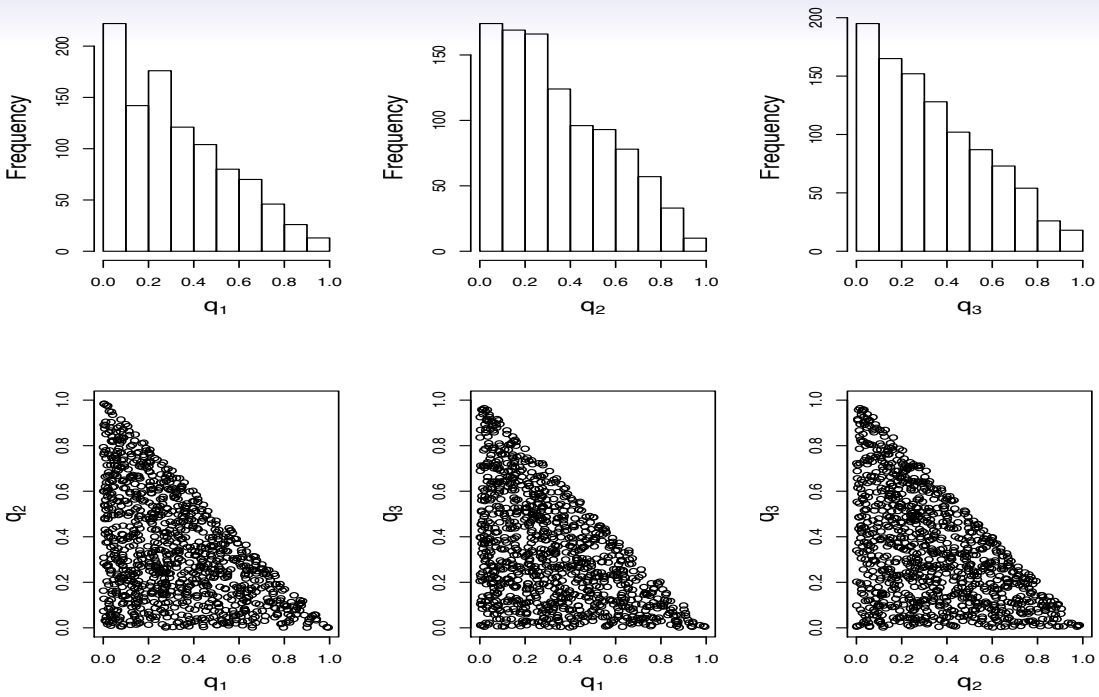



Figure 1 : Samples from a dirichlet$(1, 1, 1)$ distribution. The mean is $\left(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right)$.



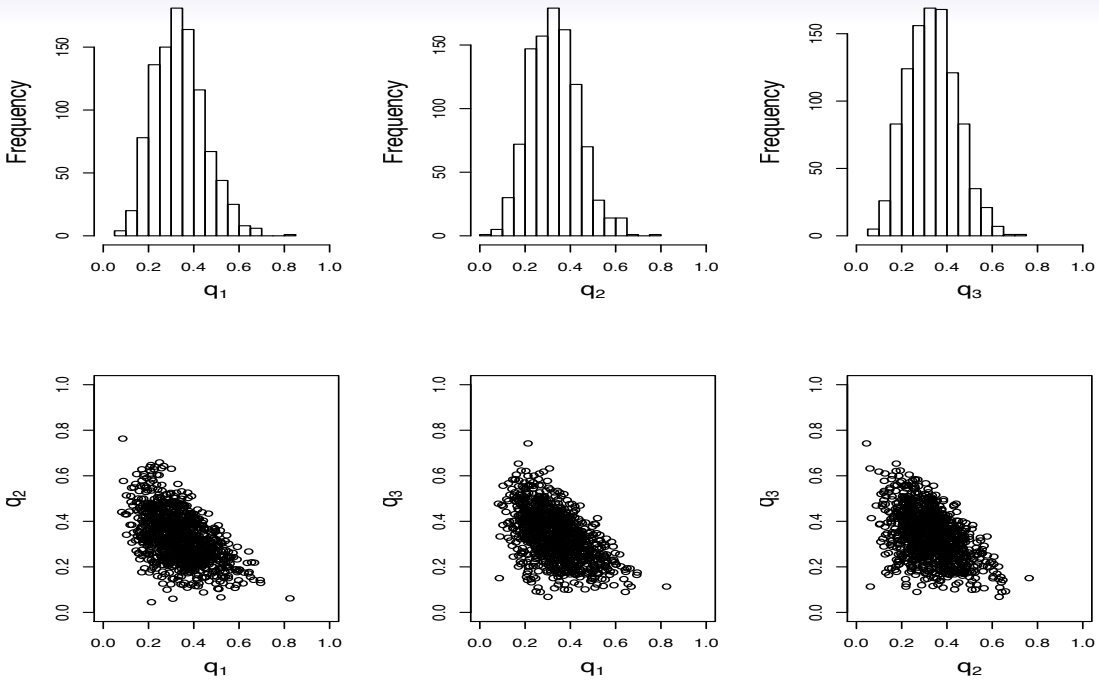



Figure 2 : Samples from a Dirichlet$(6, 6, 6)$ distribution. The mean is $\left(\frac{1}{3}, \frac{1}{3}, \frac{1}{3}\right)$.

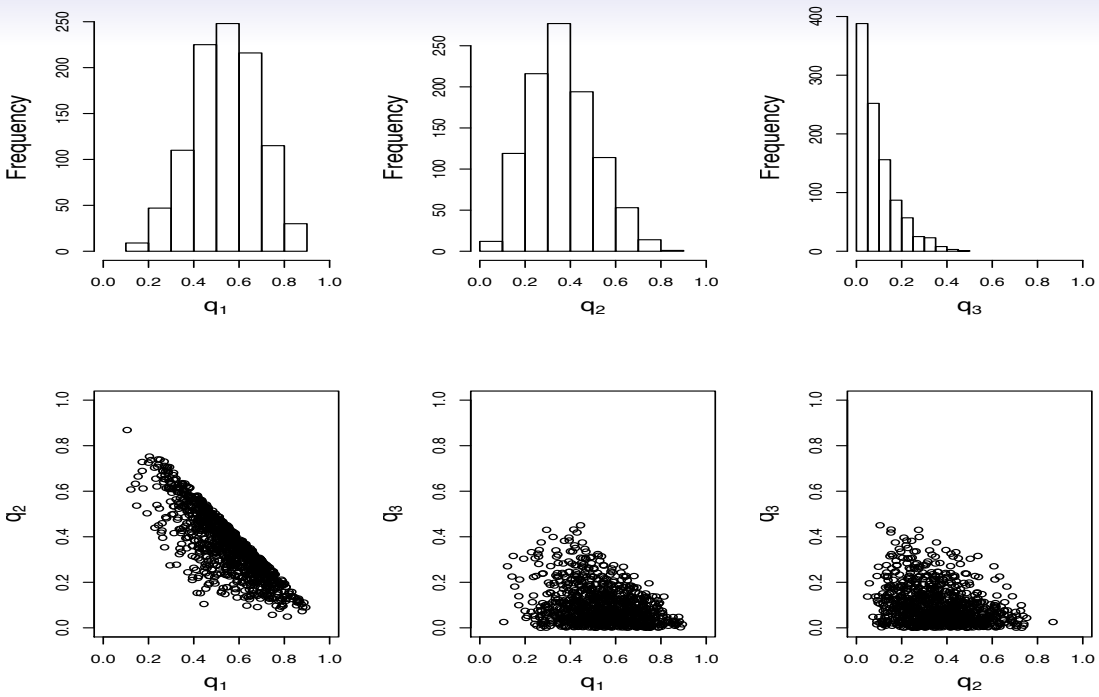



Figure 3 : Samples from a Dirichlet$(6, 4, 1)$ distribution. The mean is $(\frac{6}{11}, \frac{4}{11}, \frac{1}{11}) = (0.55, 0.36, 0.09)$.



## R Code for dirichlet(1,1,1) Sampling

- The code below produces Figure 1 which is the dirichlet(1,1,1) case.

```
> library(VGAM) # To access the rdiric function
> nsim <- 1000
> par(mfrow=c(2,3))
> q <- rdiric(nsim,c(1,1,1))
#
# Univariate marginal representations
#
> hist(q[,1],xlab=expression(q[1]),main="",cex.lab=1.5,xlim=c(0,1))
> hist(q[,2],xlab=expression(q[2]),main="",cex.lab=1.5,xlim=c(0,1))
> hist(q[,3],xlab=expression(q[3]),main="",cex.lab=1.5,xlim=c(0,1))
#
# Bivariate representations
#
> plot(q[,1],q[,2],xlim=c(0,1),ylim=c(0,1),xlab=expression(q[1]),
    ylab=expression(q[2]),cex.lab=1.5)
> plot(q[,1],q[,3],xlim=c(0,1),ylim=c(0,1),xlab=expression(q[1]),
    ylab=expression(q[3]),cex.lab=1.5)
> plot(q[,2],q[,3],xlim=c(0,1),ylim=c(0,1),xlab=expression(q[2]),
    ylab=expression(q[3]),cex.lab=1.5)
```

## Posterior Distribution

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

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

- 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 $i = 1, 2, 3$:

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

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

- The weight W is

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

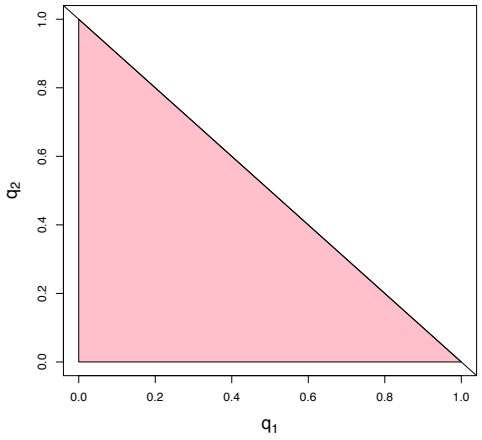
which is the proportion of the total information $(n + v)$ that is contributed by the data $(n)$.

## 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
$$n_{11} = 88, n_{12} = 10, n_{22} = 2.$$
- 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:
$$\begin{aligned} \mathrm{E}[q_1|\mathbf{n}] &= \frac{1+88}{3+100} = \frac{89}{103} \\ \mathrm{E}[q_2|\mathbf{n}] &= \frac{1+10}{3+100} = \frac{11}{103} \\ \mathrm{E}[q_3|\mathbf{n}] &= \frac{1+2}{3+100} = \frac{3}{103}. \end{aligned}$$
- 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

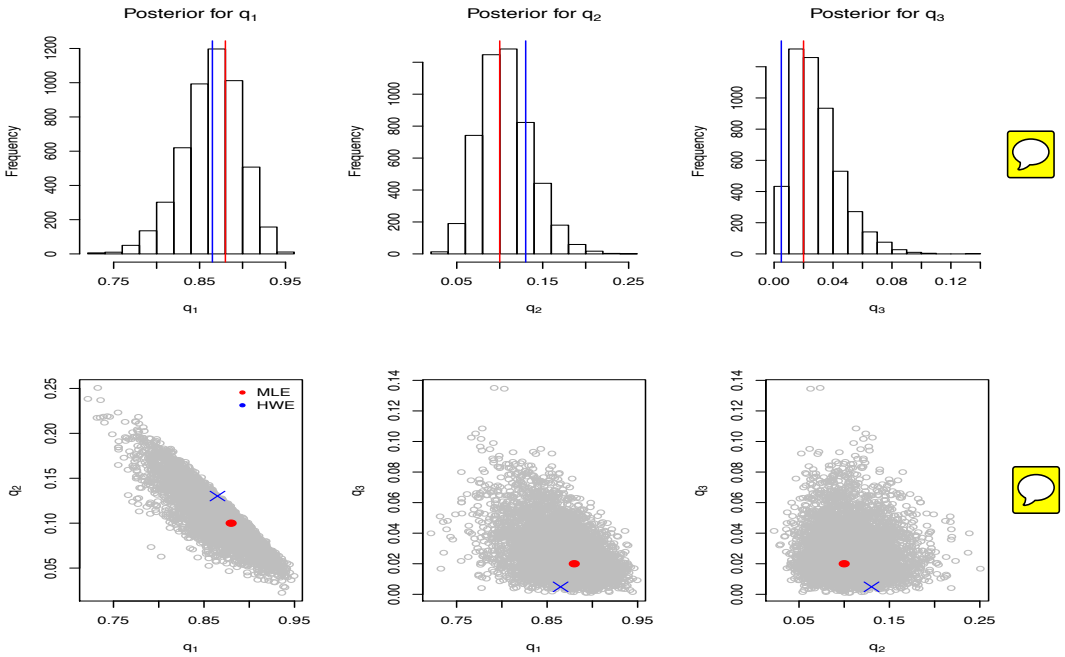



Figure 4 : Univariate and bivariate posterior distributions for $\mathbf{n} = (88, 10, 2)$. MLEs in red for the general model and in blue for the HWE model.



## R Code for Histograms in Figure 4

```
> n1 <- 88; n2 <- 10; n3 <- 2
> p1 <- 88/100 + 0.5*10/100 # Estimated allele frequencies
> p2 <- 2/100 + 0.5*10/100  # for A1 and A2
> v1 <- v2 <- v3 <- 1
> nsim <- 5000
> q <- rdiric(nsim,c(n1+v1,n2+v2,n3+v3))
> par(mfrow=c(2,3))
> hist(q[,1],xlab=expression(q[1]),
    main=expression(paste("Posterior for ",q[1])))
> abline(v=n1/(n1+n2+n3),col="red")
> abline(v=p1^2,col="blue")
> hist(q[,2],xlab=expression(q[2]),
    main=expression(paste("Posterior for ",q[2])))
> abline(v=n2/(n1+n2+n3),col="red")
> abline(v=2*p1*p2,col="blue")
> hist(q[,3],xlab=expression(q[3]),
    main=expression(paste("Posterior for ",q[3])))
> abline(v=n3/(n1+n2+n3),col="red")
> abline(v=p2^2,col="blue")
```

- 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 $\widehat{q}_i \pm 1.96 \times \text{se}(\widehat{q}_i)$ would be symmetric.

## R Code for Scatterplots in Figure 4

```
> plot(q[,2]~q[,1],xlab=expression(q[1]),ylab=expression(q[2]),
    col="grey")
> points(n1/(n1+n2+n3),n2/(n1+n2+n3),col="red",pch=20,cex=2)
> points(p1^2,2*p1*p2,col="blue",pch=4,cex=2)
> legend("topright",legend=c("MLE","HWE"),col=c("red","blue"),
      pch=c(20,20),bty="n")
> plot(q[,3]~q[,1],xlab=expression(q[1]),ylab=expression(q[3]),
    col="grey")
> points(n1/(n1+n2+n3),n3/(n1+n2+n3),col="red",pch=20,cex=2)
> points(p1^2,p2^2,col="blue",pch=4,cex=2)
> plot(q[,3]~q[,2],xlab=expression(q[2]),ylab=expression(q[3]),
    col="grey")
> points(n2/(n1+n2+n3),n3/(n1+n2+n3),col="red",pch=20,cex=2)
> points(2*p1*p2,p2^2,col="blue",pch=4,cex=2)
```

- In the context of a binomial sampling model and interest in a particular point (for example, $\theta = 0.5$) we could examine intervals for $\theta$.
- 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 coefficent:

$$D = q_1 - p_1^2$$

  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

$$\begin{aligned} q_1 &= p_1^2 + p_1(1-p_1)f \\ q_2 &= 2p_1(1-p_1)(1-f) \\ q_3 &= (1-p_1)^2 + p_1(1-p_1)f \end{aligned}$$

- Positive values of $f$ indicate an excess of homozygotes (and may indicate inbreeding), while negative values indicate an excess of heterozygotes.
- Each of $D$, $\psi$ 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 $\mathbf{q}$, dirichlet$(1,1,1)$, does not correspond to a flat prior for $D, f, \psi$, as Figure 5 shows.



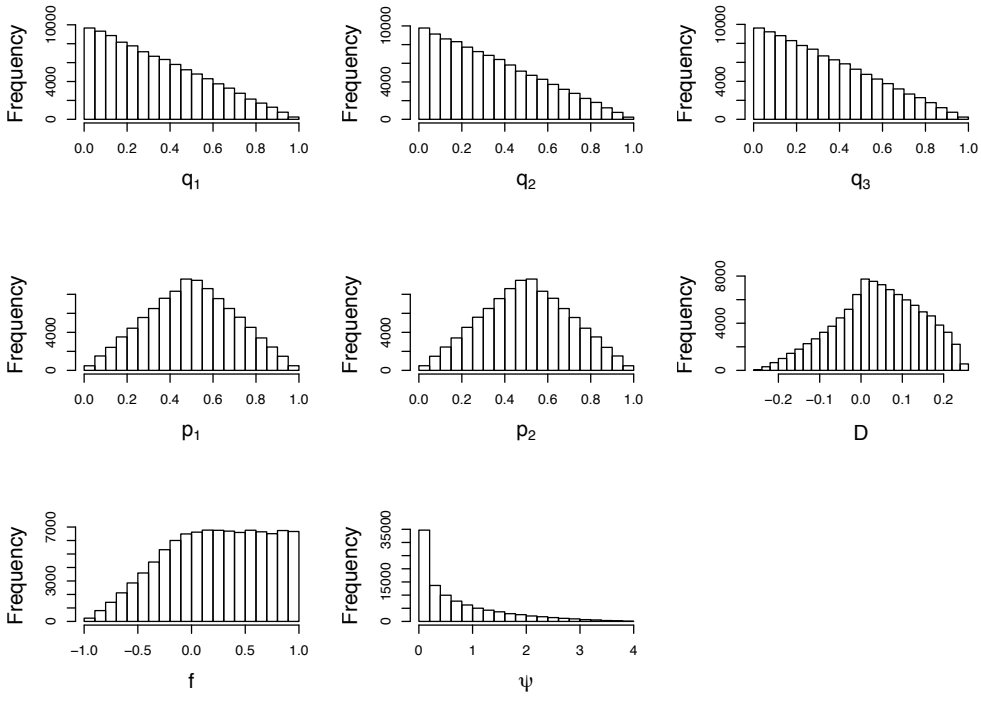



Figure 5 : Samples from a dirichlet(1,1,1) for various functions.

## R Code for Functions of Interest

- Figure 5 was created via this code, recall we simply transform the samples:

```
> v1 <- v2 <- v3 1
> nsim <- 100000
> samps <- rdiric(nsim,c(v1,v2,v3))
> q1 <- samps[,1]
> q2 <- samps[,2]
> q3 <- samps[,3]
> par(mfrow=c(3,3))
> hist(q1,main="",xlab=expression(q[1]),cex.lab=1.5)
> hist(q2,main="",xlab=expression(q[2]),cex.lab=1.5)
> hist(q3,main="",xlab=expression(q[3]),cex.lab=1.5)
> p1 <- q1+q2/2
> p2 <- q3+q2/2;
> f <- (q1-p1^2)/(p1*p2)
> D <- q1-p1^2
> psi <- q2^2/(p1*p2)
> hist(p1,main="",xlab=expression(p[1]),cex.lab=1.5)
> hist(p2,main="",xlab=expression(p[2]),cex.lab=1.5)
> hist(D,main="",xlab=expression(D),cex.lab=1.5)
> hist(f,main="",xlab="f",cex.lab=1.5)
> hist(psi,main="",xlab=expression(psi),cex.lab=1.5)
```



## 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. 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 Dir(1,1,1) the prior probability that $f > 0$ is 0.67.

```
> cat("Prior prob f>0: ",sum(f>0)/nsim,"\n")
Prior prob f>0:  0.66762
> cat("Prior prob D>0: ",sum(D>0)/nsim,"\n")
Prior prob D>0:  0.66762
```

## Bayesian Approaches to HWE

Previous 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).



## 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

$$H_0 : \text{HWE} \quad \text{versus} \quad H_1 : \text{Not HWE}.$$

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

$$\frac{\Pr(\mathbf{n}|H_0)}{\Pr(\mathbf{n}|H_1)} = \frac{\int \Pr(\mathbf{n}|p_1)p(p_1)dp_1}{\int \Pr(\mathbf{n}|q_1,q_2)p(q_1,q_2)dq_1dq_2}$$

  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,

$$\Pr(\mathbf{n}|p_1) = \Pr(n_1, n_2, n_3|p_1) = \frac{n!2^{n_1}}{n_2!n_{12}!n_3!} p_1^{2n_1+n_2}(1-p_1)^{n_2+2n_3}.$$

- With a $\text{Be}(w_1, w_2)$ prior on $p_1$:

$$\begin{aligned} \Pr(n_1, n_2, n_3|H_0) &= \int \Pr(\mathbf{n}|p_1) \times p(p_1) dp_1 \\ &= \frac{n!2^{n_2}\Gamma(w)\Gamma(2n_1+n_2+w_1)\Gamma(n_2+2n_3+w_2)}{n_1!n_2!n_3!\Gamma(w_1)\Gamma(w_2)\Gamma(2n+w)} \end{aligned} \tag{2}$$

- 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:

$$\begin{aligned} \Pr(n_1, n_2, n_3|H_1) &= \int \Pr(\mathbf{n}|q_1, q_2) \times p(q_1, q_2) dq_1 dq_2 \\ &= \frac{n!\Gamma(v)\Gamma(n_1+v_1)\Gamma(n_2+v_2)\Gamma(n_3+v_3)}{n_1!n_2!n_3!\Gamma(v_1)\Gamma(v_2)\Gamma(v_3)\Gamma(n+v)}. \end{aligned} \tag{3}$$

- 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[1].
- If 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.

[1] When we work out a $\chi^2$ 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 $n_{11} = 88, n_{12} = 10, n_{22} = 2$.
- 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 $\pi_0$, 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.
- 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

- The code below produces Figure 6.

```
> q <- rdiric(nsim,c(n1+1,n2+1,n3+1))
> q1 <- q[,1]; q2 <- q[,2]; q3 <- q[,3]
> par(mfrow=c(3,3))
> hist(q1,main="",xlab=expression(q[1]),cex.lab=1.5)
> hist(q2,main="",xlab=expression(q[2]),cex.lab=1.5)
> hist(q3,main="",xlab=expression(q[3]),cex.lab=1.5)
> p1 <- q1+q2/2; p2 <- q3+q2/2;
> f <- (q1-p1^2)/(p1*p2); D <- q1-p1^2; psi <- q2^2/(p1*p2)
> hist(p1,main="",xlab=expression(p[1]),cex.lab=1.5)
> hist(p2,main="",xlab=expression(p[2]),cex.lab=1.5)
> hist(D,main="",xlab=expression(D),cex.lab=1.5)
> hist(f,main="",xlab="f",cex.lab=1.5)
> hist(psi,main="",xlab=expression(psi),cex.lab=1.5)
```

## Posterior Inference for Functions of Interest

- Note that the asymptotic confidence interval for $f$ contains inadmissible negative values.

```
#
# MLE of f is 0.23 with asymptotic standard error 0.17
# 95% interval is
> .23-1.96*.17
[1] -0.1032
> .23+1.96*.17
[1] 0.5632
#
# Bayesian posterior quantiles are
> quantile(f,c(.025,.5,.975))
      2.5%        50%      97.5%
0.02159864 0.27112179 0.58320757
```



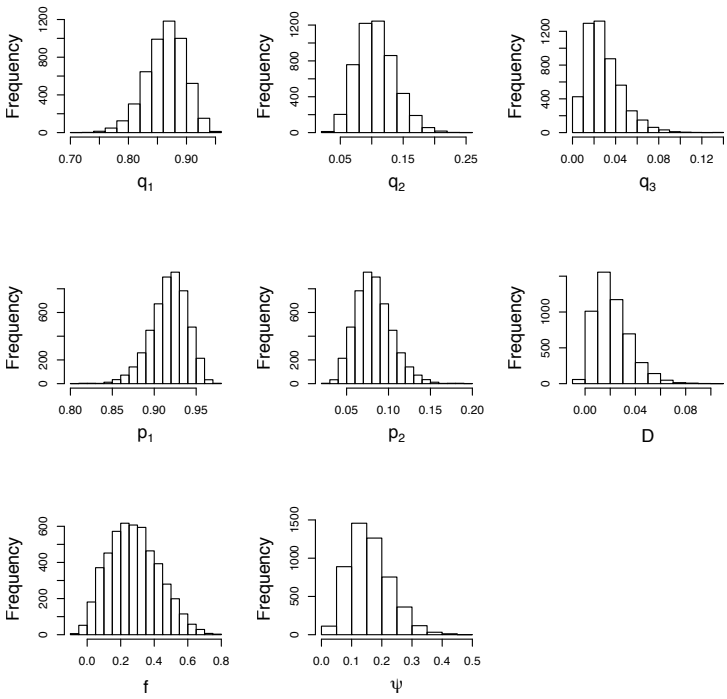



Figure 6 : Posterior inference for simple HWE example.

## 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.

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