

Does our DNA keep us awake?

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abstract

1 SNPs and insomnia

1.1 Introduction and goals

✂ [Some intro about insomnia and its symptoms here](#)

Every single-nucleotide polymorphism (SNP), together with the huge variety of external factors, can in principle affect the appearance of insomnia symptoms. It is extremely complicated to identify and untangle these causal mechanisms and interactions and to ascertain their degrees, although their causal graph (Pearl 2009) is easy to draw (fig.**). The interacting mechanisms represented by the arrows are difficult to study, and the external factors X are innumerable and largely unknown.

An indication of the causal strength of one or more SNPs on one or more symptoms can be obtained by replacing the causal graph with a corresponding simplified Bayesian network (Pearl 2009) of *conditional probabilities* (fig.**). The external factors X disappear from the graph but their presence is implicit in the probabilistic relation between the nodes; the latter also accounts for the complexity of the causal mechanisms and our uncertainty about them. This is the approach of genetic association studies ✂ ***ref.

The present work has two distinct goals:

First, we present evidence of a strong association between some SNPs located in *** and the three main insomnia symptoms ✂ [name the relevant SNPs here?](#), within population sampled in***. Our results involve associations between each symptom and several SNPs individually, and also associations between each symptom and *pairs* of SNPs; the latter result shows different kinds of interaction between the alleles of a SNP pair.

Second, we give a detailed but intuitive discussion of the Bayesian method used to infer the associations described above. Similar methods have been used for other kinds of association studies, for example contextual text prediction (MacKay et al. 1995) and population-specific allele count (Lockwood et al. 2001). This method gives simple, clear, and intuitively understandable inferences about symptom-SNP associations; it is computationally fast; and it is easy to generalize to association studies of symptom *combinations* vs *multiple* SNPs, as we'll show in later sections.

The Method section of this work focus on explaining our Bayesian approach, but use the real data from which our results are derived. In the subsequent Result section we discuss the different relevant associations found.

1.2 The data

✂ [description of our data here](#)

2 Methods

2.1 Outline

We focus on the simplest kind of association: between one particular SNP with two alleles a , b , and one insomnia symptom. For example, we could be speaking of the SNP rs875994 with alleles $a = C$, $b = T$, and onset insomnia O.

We imagine to have an arbitrarily large population from the same genetic pool as our sample. In this population we would like to know how large are the fraction $f_{|a}$ of individuals that show the symptom among those having allele a , and the fraction $f_{|b}$ that show the symptom among those having allele b . These two fractions are *conditional relative frequencies* (note that $f_{|a} + f_{|b} \neq 1$ in general, since we are not speaking about the frequencies of two mutually exclusive and exhaustive alternatives, but of frequencies *conditional* on such alternatives). ✂ [Add some remarks about the role of 'limit frequencies' and 'arbitrarily large population'? Relation to partial exchangeability and belief about next individual in an endless sequence.](#)

We are in particular interested in knowing how much these two conditional frequencies differ, that is, in $f_{|a} - f_{|b} =: \Delta f$. A larger difference may indicate some sort of biologic association between the SNP (or another

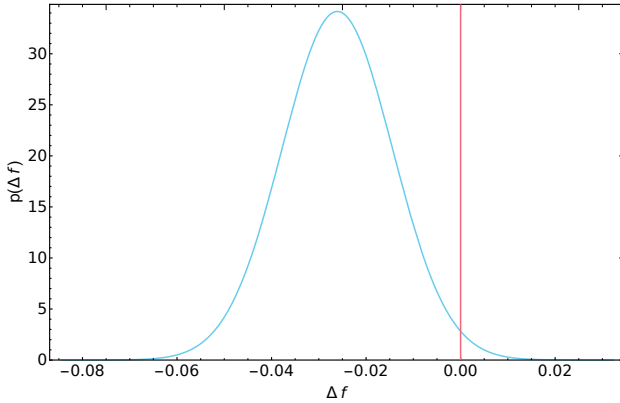


Figure 1 Example of uncertainty distribution about the conditional-frequency difference Δf

SNP linked to it) and the symptom. This difference in the large population is unknown, however; we can only make a plausible inference about its value from sampled data and other initial information. The most detailed statement we can make about it is by quantifying the distribution of our degree of belief $p(\Delta f)$ like the one plotted in fig. 1. This distribution gives us many pieces of information: for example, a negative difference Δf is more plausible than a positive one; it is 8.3% plausible that $|\Delta f| < 0.01$, and therefore 91.7% plausible that $|\Delta f| > 0.01$; it is 90% plausible that $-0.045 < \Delta f < -0.007$; and so on. Several measures can be chosen to summarize the distribution with one number. For example, we could use the plausibility that $|\Delta f|$ exceeds a given value, say $p(|\Delta f| > 0.01)$. A roughly equivalent but perhaps more preferable measure is the minimal frequency difference we are highly sure about:

$$x \text{ such that } p(|\Delta f| > x) = 0.9. \quad (1)$$

For the plot of fig. 1 such measure is 0.0112. ✂ add something about dependence of broadness on sample size, and ‘smoothing’ as discussed by MacKay & Bauman Peto (1995 § 2.6).

A more complete quantification of our uncertainty is the distribution $p(f_{|a}, f_{|b})$ among the possible joint values of the two conditional frequencies, from which $p(\Delta f)$ can be calculated. This joint distribution is also the optimal starting point when frequencies conditional on allele combinations of several SNP are considered. Our goal is therefore to

quantify this joint degree of belief, given: (1) the conditional frequencies in a population sample, (2) our initial information or guesses about such frequencies. In formulae, we want to assign a numerical value to

$$p(\text{conditional frequencies} | \text{sample data, initial information}). \quad (2)$$

In the rest of this section we shall calculate this degree of belief by methodically applying the probability calculus.

First let's observe that the approach just outlined is not dichotomous, unlike a classical significance test. We are not asking whether the frequency difference is 'significant' or not. Rather, we find a gradation of cases: from conditional frequencies likely to be very distinct, to conditional frequencies likely to be very similar. These cases can be sorted, for example with the measure of formula (1), obtaining a sequence of SNPs with a decreasing belief of causal association with the symptom. How many of these SNPs are to be selected for further study depends on one's experimental and computational resources.

2.2 Inference: concrete calculation

Once we know the quantity we want to quantify our uncertainty about, the calculation of our degrees of belief follows almost mechanically from the rules of the probability calculus (Jeffreys 1983; Cox 1946; Jaynes 2003; Hailperin 1996). This calculus also shows which degrees of belief we must provide at the start, to arrive at the desired ones.

The first step is to use Bayes's theorem:

$$p(\text{frequencies} | \text{data, initial info}) \propto$$

$$p(\text{data} | \text{frequencies, initial info}) \times p(\text{frequencies} | \text{initial info}), \quad (3)$$

which says that we need to provide two kinds of degree of belief: the plausibility of obtaining our sampled data if we had known the conditional frequencies in the larger population; and our initial guess about the conditional frequencies, before we observed the data. The first is given by a simple sampling formula. The second can be modelled in several reasonable ways; we'll see, however, that they all lead to very similar conclusions about the conditional frequencies and their

difference, owing to the large size of our sample. Let's give explicit expressions for both.

First of all, introduce some notation. The conditional frequencies are denoted $f_{|a}, f_{|b}$ as above. The data D consist in the conditional frequencies observed in the sample: $F_{|a}$ is the fraction showing the symptom among the sampled individuals having allele a , and $F_{|b}$ is the analogous fraction for allele b . Finally, our initial information I consists in our initial beliefs and in the numbers N_a, N_b of sampled individuals having allele a and b ; although these numbers are part of I we will sometimes write them explicitly besides I . (Note that N_a, N_b are not part of the 'data' in the sense that they don't help us to update our belief about the frequencies $f_{|a}, f_{|b}$ and therefore remain on the right side of the conditional.)

With this notation, Bayes's theorem above is written

$$p(f_{|a}, f_{|b} | D, I) \propto p(D | f_{|a}, f_{|b}, I) p(f_{|a}, f_{|b} | I) \equiv \\ p(F_{|a}, F_{|b} | f_{|a}, f_{|b}, N_a, N_b, I) p(f_{|a}, f_{|b} | N_a, N_b, I). \quad (3)_r$$

2.3 Plausibility for the data given the frequencies

Our degree of belief about the data given the frequencies is given by simple counting and symmetry. We have an arbitrarily large population where a fraction $f_{|a}$ of individuals having allele a show the symptom, and a fraction $1 - f_{|a}$ therefore don't show the symptom. We casually observe N_a individuals with allele a . The plausibility that a fraction $F_{|a}$ of these show the symptom is then counted as a 'drawing with replacement' because of the arbitrarily large size of the full population, given by a (rescaled) binomial distribution (Jaynes 2003 ch. 3; Ross 2010 § 4.6; Feller 1968 § VI.2):

$$p(F_{|a} | f_{|a}, N_a, I) = \binom{N_a}{N_a F_{|a}} f_{|a}^{N_a F_{|a}} (1 - f_{|a})^{N_a (1 - F_{|a})}. \quad (4)$$

An analogous reasoning holds for allele b . Our belief about obtaining the data is therefore

$$p(D | f_{|a}, f_{|b}, I) = \prod_{x=a,b} \binom{N_x}{N_x F_{|x}} f_{|x}^{N_x F_{|x}} (1 - f_{|x})^{N_x (1 - F_{|x})}. \quad (5)$$

2.4 Initial plausibility for the frequencies

We consider two different initial assumptions about the conditional frequencies. Their densities are represented in fig. 2. The first (left plot) assigns equal plausibility to equal areas in the $(f_{|a}, f_{|b})$ -coordinate plane; we call this the ‘uniform’ state of knowledge and denote it I_u . The second (right plot) expresses a strong belief that the two frequencies should be equal, as clear from the steep density increase towards the diagonal of the $(f_{|a}, f_{|b})$ -coordinate plane; we call this a ‘conservative’ state of knowledge and denote it I_c .

The uniform state of knowledge is given by the simple density

$$p(f_{|a}, f_{|b} | I_u) = 1. \quad (6)$$

The conservative state of knowledge is given by the following integral:

$$p(f_{|a}, f_{|b} | I_c) = \int_0^\infty du \int_0^\infty dv \, p(f_{|a}, f_{|b} | u, v, I_c) \, p(u, v | I_c) \quad (7a)$$

with

$$p(f_{|a}, f_{|b} | u, v, I_c) := \beta(f_{|a} | u, v) \, \beta(f_{|b} | u, v), \quad (7b)$$

$$p(u, v | I_c) := \frac{1}{u + v} \, \gamma(u + v | 1, 1000) \quad (7c)$$

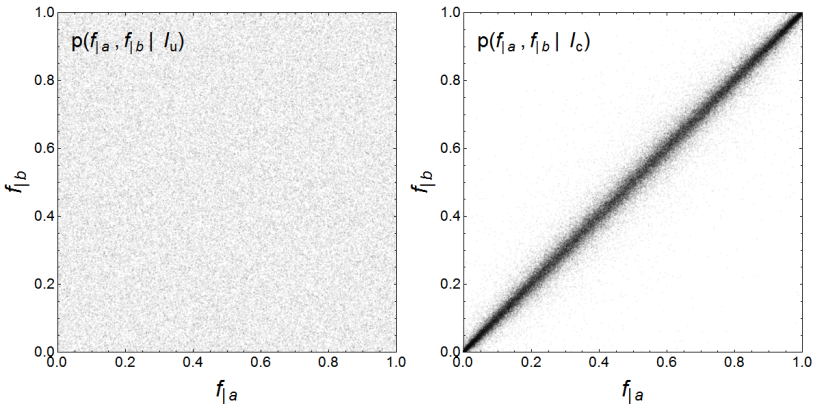


Figure 2 Qualitative plot of our initial beliefs

where β and γ are beta and gamma densities:

$$\beta(f|u, v) := \frac{\Gamma(u+v)}{\Gamma(u)\Gamma(v)} f^{u-1} (1-f)^{v-1}, \quad u, v > 0, \quad (7d)$$

$$\gamma(\alpha|1, 1000) := \frac{1}{1000} \exp(-\alpha/1000). \quad (7e)$$

The integral expression (7) can be interpreted as follows: we consider several independent beliefs about of the two frequencies (the product of beta densities, depending on identical shape parameters), and then weigh and mix them together to arrive at a belief that is not independent about the two frequencies. This also corresponds to defining a so-called hierarchic model (Good 1980). The particular shape and scale values of the gamma density are chosen so as to concentrate our initial belief along the $(f_{|a}, f_{|b})$ diagonal; this choice has also a deeper interpretation, discussed in appendix***.

We will examine how much our conclusions about the frequencies differ between the two initial states of knowledge. Note that the second is indeed very conservative. Therefore, if our updated belief conditional on the data will show clearly distinct conditional frequencies, it will be because the data have given enough evidence to overwhelm this conservative belief.

2.5 Final plausibilities

Now we have the plausibility (5) for the sampled data, and two choices of initial plausibilities (6), (7), and we can multiply and renormalize these in Bayes's theorem (3) to obtain our final degrees of belief.

In the case of the uniform initial state of knowledge, multiplication of the sampling formula (5) and initial degree of belief (6) leads to a density for the frequencies proportional to the product of two beta densities. Our final degree of belief in this case is

$$p(f_{|a}, f_{|b}|D, I_u) = \prod_{x=a,b} \beta[f_{|x}|N_x F_{|x} + 1, N_x (1 - F_{|x}) + 1] \quad (8)$$

This is the product of two independent beliefs about the frequencies.

In the case of the conservative initial state of knowledge, multiplication of (5) and the beta densities within the integral of eq. (7) leads to two new unnormalized beta densities. Grouping the ensuing normalization

constant with the density for the parameters (7c) yields a final degree of belief in integral form:

$$p(f_{|a}, f_{|b} | D, I_c) = \int_0^\infty du \int_0^\infty dv \prod_{x=a,b} \{\beta[f_{|x} | N_x F_{|x} + u, N_x (1 - F_{|x}) + v]\} p(u, v | D, I_c) \quad (9a)$$

with

$$p(u, v | D, I_c) \propto \prod_{x=a,b} \left\{ \frac{\Gamma(N_x F_{|x} + u) \Gamma[N_x (1 - F_{|x}) + v]}{\Gamma(N_x + u + v)} \frac{\Gamma(u + v)}{\Gamma(u) \Gamma(v)} \right\} \frac{\gamma(u + v | 1, 1000)}{u + v}. \quad (9b)$$

This is a hierarchic model. The integral doesn't have an analytic form, but the final density for the frequencies can be sampled by generating samples of the shape parameters u, v from (9b) via Markov-Chain Monte Carlo methods, and for each generating samples of the frequencies from the beta densities with those shape parameters (alternatively we can write an averaged sum of beta distributions having the sampled shape parameters).

Thanks to the large sample sizes N_a, N_b the final densities above can be well approximated by normal densities. We only need to determine their means and covariance matrices. These can be easily calculated using the first and second raw moments of a beta distribution:

$$E(f | u, v) = \frac{u}{u + v}, \quad E(f^2 | u, v) = \frac{u(u + 1)}{(u + v)(u + v + 1)}. \quad (10)$$

For the uniform initial state of knowledge (8) the means, variances, and covariance are readily calculated:

$$E(f_{|x} | D, I_u) = \frac{N_x F_{|x} + 1}{N_x + 2}, \quad \frac{N_b F_{|b} + 1}{N_b + 2}, \quad x = a, b \quad (11a)$$

$$\text{var}(f_{|x} | D, I_u) = \frac{(N_x F_{|x} + 1) [N_x (1 - F_{|x}) + 1]}{(N_x + 2)^2 (N_x + 3)}, \quad x = a, b \quad (11b)$$

$$\text{cov}(f_{|a}, f_{|b} | D, I_u) = 0. \quad (11c)$$

The covariance vanishes owing to the product form of the final density.

For the conservative initial state of knowledge (9) let us first introduce the notation

$$\langle X(u, v) \rangle := \int_0^\infty du \int_0^\infty dv X(u, v) p(u, v | D, I_c); \quad (12)$$

such an average can approximately be computed by averaging from a Monte Carlo sample. The means, variances, and covariance of the final density are

$$E(f_{|x} | D, I_c) = \left\langle \frac{N_x F_{|x} + u}{N_x + u + v} \right\rangle, \quad x = a, b, \quad (13a)$$

$$\text{var}(f_{|x} | D, I_u) = \left\langle \frac{(N_x F_{|x} + u)(N_x F_{|x} + u + 1)}{(N_x + u + v)(N_x + u + v + 1)} \right\rangle - \left\langle \frac{N_x F_{|x} + u}{N_x + u + v} \right\rangle^2, \\ x = a, b \quad (13b)$$

$$\text{cov}(f_{|a}, f_{|b} | D, I_u) = \\ \left\langle \frac{N_a F_{|a} + u}{N_a + u + v} \frac{N_b F_{|b} + u}{N_b + u + v} \right\rangle - \left\langle \frac{N_a F_{|a} + u}{N_a + u + v} \right\rangle \left\langle \frac{N_b F_{|b} + u}{N_b + u + v} \right\rangle. \quad (13c)$$

The covariance does not vanish owing to our initial correlated beliefs about the two conditional frequencies, but is generally reduced by the sample data.

2.6 Plausibilities for the frequency differences

$$E(f_{|a} - f_{|b} | D, I) = E(f_{|a} | D, I) - E(f_{|b} | D, I) \quad (14)$$

$$\text{var}(f_{|a} - f_{|b} | D, I) = \text{var}(f_{|a} | D, I) + \text{var}(f_{|b} | D, I) - 2 \text{cov}(f_{|a}, f_{|b} | D, I) \quad (15)$$

2.7 Generalization to symptom combinations

2.8 Choices of initial beliefs and meaning of the parameters

The parameters u of the Dirichlet density for the frequency distribution f have very intuitive meanings, even more evident if we rewrite them as their sum and a pair of normalized parameters:

$$\alpha := \sum u, \quad \mathbf{v} := u / \sum u. \quad (16)$$

The normalized parameters \mathbf{v} are the expected frequency distribution:

$$E(f|\mathbf{u}) = \mathbf{v} \quad (17)$$

The sum of the parameters α expresses the sharpness of the distribution, as seen from the covariance matrix:

$$\text{var}(f_i|\mathbf{u}) = \frac{v_i(1-v_i)}{\alpha+1}, \quad \text{cov}(f_i f_j|\mathbf{u}) = -\frac{v_i v_j}{\alpha+1}. \quad (18)$$

In fact, from the update formula*** we see that α quantifies the amount of data necessary to modify our initial belief.

$$\frac{E(f_{O|a} - f_{O|b}|D, I)}{\sigma(f_{O|a} - f_{O|b}|D, I)}$$

3 Results

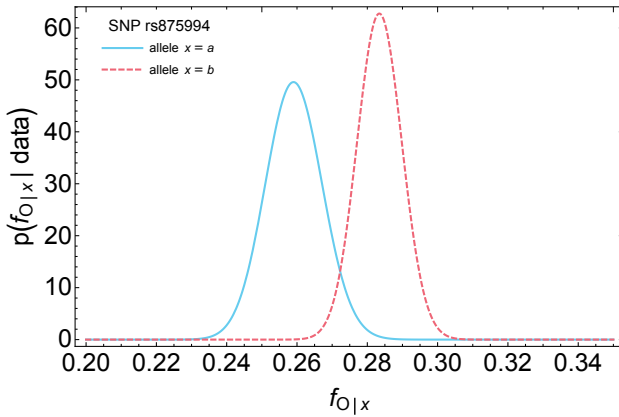


Figure 3 Example of distributions of belief

Appendices

This construction has the interesting consequence for our updated belief $p(f_{|a}, f_{|b} | D, I)$. According to Bayes's theorem (3) combined with our initial belief (??) it is given by

$$p(f_{|a}, f_{|b} | D, I) \propto p(D | f_{|a}, f_{|b} | I) p(f_{|a}, f_{|b} | I), \quad (19)$$

but, as shown in appendix A, it can also be written in the following way:

$$p(f_{|a}, f_{|b} | D, I) = \int du \int dv p(f_{|a}, f_{|b} | D, u, v, I) \pi(u, v | D, I), \quad (20)$$

with the normalized density $\pi(u, v | D, I)$ defined by

$$\begin{aligned} \pi(u, v | D, I) &\propto \pi(u, v | I) \times \\ &\underbrace{\int df_{|a} \int df_{|b} p(D | f_{|a}, f_{|b}, I) p(f_{|a}, f_{|b} | u, v, I)}_{=: p(D | u, v, I)}. \end{aligned} \quad (21)$$

It is as if u, v were unknown parameters with initial belief density $\pi(u, v | I)$, and our update for the frequencies proceeded by first updating our belief about the parameters, eq. (21), and then marginalizing them out, eq. (20). This is a so-called *hierarchic* model (Good 1980). This hierarchic way of thinking often helps in constructing densities that

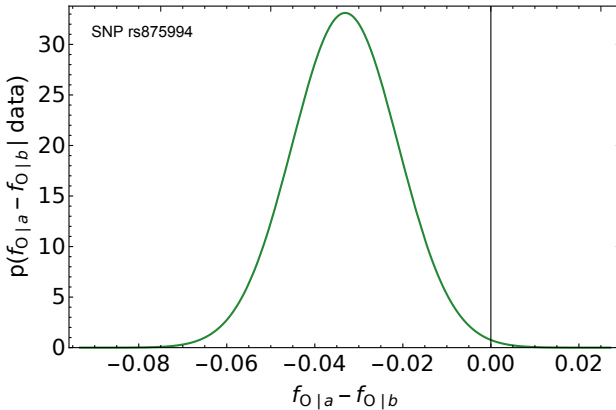


Figure 4 Distribution for the difference between the frequencies $f_{0|a}, f_{0|b}$ of onset insomnia (O) conditional on the two alleles of SNP rs875994

better represent our initial beliefs, and also leads to formulae that can be better approximated when exact computation is unfeasible. A point rarely emphasized in the literature, though, is that there is no mathematical difference between a hierarchic and a non-hierarchic model: we could forget about the integrals in formula (??) and about the update formula (20), and simply treat $p(f_{|a}, f_{|b} | I)$ as the density depicted in fig. ??, with update (3). The results would be the same. Further discussion about the formulae above is given in §***.

With large sample sizes the density $\pi(u, v | D, I)$ turns out to be so peaked with respect to $p(f_{|a}, f_{|b} | u, v, I)$ that it can be considered as a Dirac delta centred on the parameters u_M, v_M that maximize it. We thus obtain a good approximation of the updated belief (20) that doesn't involve parameter integration:

$$p(f_{|a}, f_{|b} | D, I) \approx p(f_{|a}, f_{|b} | u_M, v_M, I) \\ \text{with } (u_M, v_M) := \arg \max_{u, v} \pi(u, v | D, I). \quad (22)$$

The maximum of $\pi(u, v | D, I)$, or better of its logarithm, can easily be found with most optimization methods. The explicit expression to be optimized, discussed in appendix***,

$$k [\ln \Gamma(\sum_s \mathbf{u}_s) - \sum_s \ln \Gamma(\mathbf{u}_s)] - \sum_{x=a, b} [\ln \Gamma(N_x + \sum_s \mathbf{u}_s) - \sum_s \ln \Gamma(N_x F_{s|x} + \mathbf{u}_s)] \quad (23)$$

A Derivation of Bayes's theorem in hierarcic form

We write Bayes's theorem (19) with our initial belief (??) written in full:

$$p(f_{O|a}, f_{O|b} | D, I) \propto \int d\alpha \int d\mathbf{v} p(D | f_{O|a}, f_{O|b} | I) p(f_{O|a}, f_{O|b} | \alpha, \mathbf{v}, I) \pi(\alpha, \mathbf{v} | I). \quad (24)$$

Multiplying and dividing within the integral with the expression

$$p(D | \alpha, \mathbf{v}, I) := \int df_{O|a} \int df_{O|b} p(D | f_{O|a}, f_{O|b}, I) p(f_{O|a}, f_{O|b} | \alpha, \mathbf{v}, I) \quad (25)$$

we obtain the alternative form (20)

Combining together the sampling formula (5), the expression of the beta density (7d), and the update formula (21) we obtain

$$\pi(\alpha, \mathbf{v} | D, I) \propto \pi(\alpha, \mathbf{v}) \times \left[\int \mathrm{d}f_{O|a} \int \mathrm{d}f_{O|b} \beta\left(f_{O|a} | \alpha + N_a, \frac{\alpha \mathbf{v} + N_a F_{O|a}}{\alpha + N_a}\right) \beta\left(f_{O|b} | \alpha + N_b, \frac{\alpha \mathbf{v} + N_b F_{O|b}}{\alpha + N_b}\right) \right] \quad (26)$$

B Summary of the main formulae

We have a sample of size n . We check the subsample of individuals that have a particular allele, say Bx, for a particular gene, say rs697680_A. Suppose that in this subsample n_0 individuals *don't* show symptom A and n_1 *do* show symptom A. This also means that the size of our subsample (individuals with allele Bx) is $n := n_0 + n_1$.

Our degree of belief about the frequency f_1 of symptom A among the individuals with allele Bx in an *infinite* population is a Beta distribution with parameters $n_0 + \theta_0$, $n_1 + \theta_1$, with $\theta := \theta_0 + \theta_1$:

$$p(f_1 | n_0, n_1, \theta_0, \theta_1) \mathrm{d}f_1 = \frac{\Gamma(n + \theta)}{\Gamma(n_0 + \theta_0) \Gamma(n_1 + \theta_1)} (1 - f_1)^{n_0 + \theta_0 - 1} f_1^{n_1 + \theta_1 - 1} \mathrm{d}f_1 \quad (27)$$

This distribution has expected value and variance

$$\begin{aligned} E(f_1 | n_0, n_1, \theta_0, \theta_1) &= \frac{n_1 + \theta_1}{n + \theta}, \\ \text{var}(f_1 | n_0, n_1, \theta_0, \theta_1) &= \frac{(n_0 + \theta_0)(n_1 + \theta_1)}{(n + \theta)^2 (n + \theta + 1)}. \end{aligned} \quad (28)$$

✂ Possible further developments: use of hyper-Dirichlet priors, use of graphical models to infer causal relationships (Pearl 2009)

$$\begin{aligned}
p(f|D) &\propto p(D|f) p(f|I) \\
&\propto p(D|f) \int du p(f|u) p(u|I) \\
&\propto \int du p(D|f) p(f|u) p(u|I) \\
&\propto \int du p(D|f, u) p(f|u) p(D|u) p(u|I) \\
&\propto \int du p(f|D, u) p(u|D) \\
p(u|D) &\propto \int df p(D|f) p(f|u) p(u|I) \\
&\propto \prod_{x=a,b} \left[\frac{\Gamma(\sum_s u_s)}{\prod_s \Gamma(u_s)} \frac{\prod_s \Gamma(N_x F_s | x + u_s)}{\Gamma(N_x + \sum_s u_s)} \right] \\
p(f_{O|a}, f_{O|b} | D, I) &\approx p(f_{O|a}, f_{O|b} | u_M, v_M, I)
\end{aligned}$$

Thanks

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- (‘de X ’ is listed under D , ‘van X ’ under V , and so on, regardless of national conventions.)
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