

# Do genes keep us awake?

## Research notes

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## 1 Preliminary remarks about Bayesian probability theory

Bayesian probability theory is not just a set of new, better recipes meant to replace old ones. It also requires a different – and simpler – mindset about problems of inference. Three points are especially important:

1. The only purpose of Bayesian theory is to give the probability of some statements – more exactly, ‘propositions’ (Copi et al. 2014; Barwise et al. 2003) – given other statements that may concern data, facts, hypotheses. For example, Bayesian theory can tell us that hypothesis  $A$  has probability  $x$  given some data  $D$  and initial information  $I$ , while hypothesis  $B$  has probability  $y$  given the same conditions:

$$P(A|D, I) = x, \quad P(B|D, I) = y.$$

That’s all there is to it. We can then use these probabilities as we like; in particular, we can use them within decision theory to choose courses of action (Raiffa et al. 2000; Pratt et al. 1996; Sox et al. 2013). But notions like ‘statistical significance’, ‘acceptance level’, ‘confidence’, and similar are foreign to Bayesian theory; or at best they’re just secondary notions.

2. Bayesian theory is an extension of formal logic, the truth calculus. In fact we’ll call it *probability calculus* from now on.

In formal logic, to prove a theorem we need some axioms to start from. These may partly include experimental facts or data, but they always also include assumptions that are purely conjectural. It’s impossible to avoid

this conjectural element (see for example Harding 1976).<sup>1</sup> Likewise, in the probability calculus we need to specify initial probabilities. These may originate in data, but they always also include additional assumptions. The motto ‘let the data speak for themselves’ is simply impossible.

The difference between Bayesian methods and traditional methods is *not* that the former need additional assumptions while the latter don’t. Rather, Bayesian methods make these assumptions explicit, while traditional methods hide them. This is the reason why many traditional results can be obtained as special cases of Bayesian ones.

3. Conditional probabilities like  $P(A|B)$  do not express a causal connection between  $A$  and  $B$ , but an *informational* connection. In that conditional probability,  $A$  could be the cause of  $B$ , or  $B$  of  $A$ , or neither could be the cause of the other. The classical example of this is

$$P(\text{clouds in the sky} | \text{rain on the pavement}, I) > 0.5, \quad (1)$$

not because the rain is the cause of the clouds, but because its presence gives us *relevant information* about the cloudiness of the sky.

The previous remarks may appear pedantic, but they’re important lest we misuse Bayesian methods.

## 2 What is the question?

✧ Luca: the following thoughts may be naive; I must still read (Stingo et al. 2015) and (Bush et al. 2012)

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<sup>1</sup>This impossibility is well known in modern science; we can quote Poincaré (1992): ‘But upon more reflection we realize the position held by hypothesis; we see that the mathematician wouldn’t know how to do without it, and the experimenter can’t do without it at all’ (Introduction); ‘Every generalization is a hypothesis’ (ch. IX, p. 176). Duhem (1991): ‘In sum, the physicist can never subject an isolated hypothesis to experimental test, but only a whole group of hypotheses; when the experiment is in disagreement with his predictions, what he learns is that at least one of the hypotheses constituting this group is unacceptable and ought to be modified; but the experiment does not designate which one should be changed’ (§ VI.2, p. 187); ‘Unlike the reduction to absurdity employed by geometers, experimental contradiction does not have the power to transform a physical hypothesis into an indisputable truth; in order to confer this power on it, it would be necessary to enumerate completely the various hypotheses which may cover a determinate group of phenomena; but the physicist is never sure he has exhausted all the imaginable assumptions’ (§ VI.3, p. 190); ‘the realization and interpretation of no matter what experiment in physics imply adherence to a whole set of theoretical propositions’ (§ VI.5, p. 200). Medawar (1963): ‘the starting point of induction, naive observation, innocent observation, is a mere philosophic fiction. There is no such thing as unprejudiced observation’ Jeffreys [quote][ref].

We want to assess the informational relevance between some genetic variations  $\{G\}$  and (combinations of) insomnia symptoms  $\{S\}$  in the Norwegian or European population. To assess this relevance we use data  $D$  from a population sample. Some assumptions or background information  $I$  are also always present in our assessment.

The most common approach in this kind of problems is to set two hypotheses against each other: ‘there is a correlation’ vs ‘there isn’t a correlation’, and to assess which is more probable in view of the data. Mathematically this corresponds to a dichotomy between an exactly zero value and non-zero values of a correlation-like quantity. We’d like to approach this problem differently. Rather than contrasting zero against non-zero values, we simply calculate that value. ✂ check (Stephens et al. 2009): they seem to have a reference with a similar philosophy

The most straightforward way to assess the informational relevance of a genetic variation  $G$  for the insomnia symptom  $S$  is to compare  $P(S|G DI)$  and  $P(S|DI)$ . If these two probabilities are approximately equal then the particular genetic variation  $G$  are *informationally* irrelevant for our prediction of the insomnia symptom  $S$ . The same conclusion holds with  $G$  and  $S$  exchanged: the probability calculus says that

$$P(S|G DI) = P(S|DI) \iff P(G|S DI) = P(G|DI) \quad (2)$$

if  $P(S|DI)$ ,  $P(G|DI)$  aren’t zero.

This measure of relevance can be extended to sets of (combinations of) symptoms  $\{S\}$  and of genetic variations  $\{G\}$  by using the conditional entropy (Cover et al. 2006 ch. 2)

$$H(\{S\}|\{G\}, DI) := - \sum_G P(G|DI) \sum_S P(S|G DI) \ln P(S|G DI), \quad (3)$$

which is zero only if  $G$  gives us certainty about  $S$ , and is equal to the entropy

$$H(\{S\}|DI) := - \sum_S P(S|DI) \ln P(S|DI) \quad (4)$$

if  $G$  is irrelevant for predicting  $S$  (Cover et al. 2006 ch. 2).

If we find that there is a mutual informational relevance between genetic variations and insomnia symptoms, we can conclude from biologic reasons that those variations must have a direct or indirect influence on the symptoms, for example they may give susceptibility to insomnia.

There are three main ways to calculate the conditional probabilities of above: By calculating first  $P(SG|DI)$ , or  $P(S|GDI)$ , or  $P(G|SDI)$ . Also, we can consider all possible combinations of genetic variations from the outset, or consider combination of few variations, gradually increasing the numbers. We shall try all these approaches and see whether their results are mutually consistent.

### 3 Why exchangeability

The sentence ‘the probability for an insomnia symptom given a genetic variation’ is vague. What we mean is our guess that a given individual with that variation presents that symptom. Our guess about a particular individuals in the full population is updated from our knowledge about individuals we have sampled. Our guess about a new individual is affected by the sample data only insofar we believe those data to be representative for that individual.

The notion of exchangeability expresses this representativeness in probabilistic terms, as explained at length by de Finetti (1931; 1937; 1938). Denote by  $S_s^{(i)}$  the statement that individual  $i$  has symptom  $S_s$ , and likewise with  $G_g^{(i)}$  for the combination of genetic variations  $g$ . The fact that we believe, for inferential purposes, that the individuals from a population having the same genetic variation  $g$  are representative of one another is expressed by

$$P(S_{s_1}^{(1)} S_{s_2}^{(2)} S_{s_3}^{(3)} \dots | G_g^{(1)} G_g^{(2)} G_g^{(3)} \dots I) = P(S_{s_{\pi(1)}}^{(1)} S_{s_{\pi(2)}}^{(2)} S_{s_{\pi(3)}}^{(3)} \dots | G_g^{(1)} G_g^{(2)} G_g^{(3)} \dots I) \quad (5)$$

where  $\pi$  is an arbitrary permutation of the individuals’ labels  $i$ . For example,

$$P(S_c^{(1)} S_a^{(2)} S_b^{(3)} \dots | G_g^{(1)} G_g^{(2)} G_g^{(3)} \dots I) = P(S_b^{(1)} S_c^{(2)} S_a^{(3)} \dots | G_g^{(1)} G_g^{(2)} G_g^{(3)} \dots I). \quad (6)$$

This mathematical property is called *exchangeability*. If the number of individuals is finite it is called *finite* exchangeability; letting this number increase indefinitely we reach *infinite* exchangeability as a limit (Heath et al. 1976).

Assuming exchangeability for each group of individuals sharing the same genetic variation, the mathematical relations above generalize as follows. Our probability assignment is the same if we exchange symptom labels among individuals *having the same genetic variation*; but it may be different if we exchange symptom labels among individuals with different genetic variations. The exact mathematical expression may look complicated; a concrete example is

$$P(S_a^{(1)} S_c^{(2)} S_d^{(3)} S_a^{(4)} S_b^{(5)} S_d^{(6)} \dots | G_\alpha^{(1)} G_\beta^{(2)} G_\beta^{(3)} G_\gamma^{(4)} G_\alpha^{(5)} G_\gamma^{(6)} \dots I) = \\ P(S_b^{(1)} S_d^{(2)} S_c^{(3)} S_d^{(4)} S_a^{(5)} S_a^{(6)} \dots | G_\alpha^{(1)} G_\beta^{(2)} G_\beta^{(3)} G_\gamma^{(4)} G_\alpha^{(5)} G_\gamma^{(6)} \dots I) \quad (7)$$

where the probability remains the same as we exchange symptoms  $a$  and  $b$  between individuals 1 and 5, both having genetic variation  $\alpha$ ; symptoms  $c$  and  $d$  between individuals 2 and 3, both having genetic variation  $\beta$ ; symptoms  $a$  and  $d$  between individuals 4 and 6, both having genetic variation  $\gamma$ . These exchanges can involve an arbitrary number of individuals, symptoms, genetic variations. This general property is called *partial* exchangeability (de Finetti 1938; Diaconis et al. 1980; Diaconis 1988; for a connection with sampling theory see Sugden 1982; 1993).

Note that the property exemplified by eq. (7) is more general than just separately stating exchangeability for the probability distributions for the individuals sharing the same genetic variations. Property (7) allows data about individuals with a genetic variation to be *relevant* for prediction of data about individuals with *another* genetic variation, as we'll see shortly.

✚ add: de Finetti's representation theorem for probability distributions with the property above

## 4 Selection of variables and robustness

Denote the presence of the genetic variation labelled  $i$  by  $G_i$  and its absence by  $\neg G_i$ . We can consider the relevance of each variation individually, say

$$P(S | G_1 DI), \quad (8)$$

or of the combination of any number of variations, say

$$P(S | G_1 \neg G_2 \neg G_3 G_4 DI). \quad (9)$$

The probability calculus allows us to assign all these probabilities for any amount of data  $D$  – since they represent beliefs. If the number of combinations is high compared with the number of data, however, these probabilities will usually change noticeably when updated with new data; we can say that they are less ‘robust’ to the acquisition of new data. This robustness can be quantified in various ways to be discussed later.

From this point of view it makes sense to first consider each genetic variation individually and then larger and larger combinations of variations, as long as we see that our probabilities conditional on data  $D$  are robust.

✠ Jeffreys (1983) § 3.2 *very* relevant to our problem! Also Broad (1918)

✠ See Jeffreys (1983 § 3.1, p. 124) on the probability to be given to the ratio values  $\{0, 1\}$ : ‘In genetics the suggested values are usually intermediate, such as  $1/2$ ,  $1/4$ , and  $3/8$ ’. Also, ‘we cannot give a universal rule for them beyond the common-sense one, that if anybody does not know what his suggested value is, or whether there is one, he does not know what question he is asking and consequently does not know what his answer means.’

## 5 Approach via the joint probability

**Notation** The following notation produces compact but readily understandable formulae. Functions and operations on tuples  $\mathbf{x} := (x_1, \dots, x_D)$ ,  $\mathbf{y} := (y_1, \dots, y_D)$ , and numbers  $a$  operate component-wise. For example:

$$\begin{aligned} \exp \mathbf{x} &:= (\exp x_1, \dots, \exp x_D) & \mathbf{x} \mathbf{y} &:= (x_1 y_1, \dots, x_D y_D) \\ a \mathbf{x} &:= (ax_1, \dots, ax_D) & \mathbf{x}^a &:= (x_1^a, \dots, x_D^a) \quad \text{and so on.} \end{aligned} \quad (10a)$$

The exception are the sum and multiplication operators  $\sum, \prod$ :

$$\sum \mathbf{x} := x_1 + \dots + x_D \quad \prod \mathbf{x} := x_1 \cdots x_D \quad (10b)$$

so that, for example,

$$\sum \ln(\mathbf{x}/\mathbf{y}) := \sum_{i=1}^D \ln(x_i/y_i).$$

Note also the convention

$$\binom{a}{\mathbf{x}} := \binom{a}{x_1, \dots, x_D} := \frac{a!}{x_1! \cdots x_D!} \quad \prod \binom{\mathbf{y}}{\mathbf{x}} := \binom{y_1}{x_1} \cdots \binom{y_D}{x_D}, \quad (10c)$$

where the first expression is the multinomial coefficient.

We approach our problem first using finite exchangeability: we are sampling from the Norwegian or European population.

Denote by  $N$  the amount of Norwegian or European population, roughly equal to  $5.3 \times 10^6$  or  $740 \times 10^6$ . Our initial information is that each individual is characterized by an insomnia parameter  $s \in \{1, \dots, 8\}$  and  $v := 94$  gene allele pairs, whose combinations are denoted  $g := (g_1, \dots, g_v) \in \{0, 1\}^v$ . The combined variate  $x := (s, g)$  can thus assume  $D := 8 \times 2^{94} \approx 1.6 \times 10^{29}$  possible values.

Suppose that the relative distribution of the variate  $x$  in the whole population is  $F$ , where  $F$  has  $D$  components and  $\sum F = 1$ ; that is,  $NF_x$  individuals have value  $x$  for this variate. There are  $\binom{N+D-1}{D-1}$  possible distributions (Csiszár et al. 2004 § 2.1). Most components of  $F$  vanish because there are vastly more variate values than individuals. The probability that a sample of  $n$  individuals has a relative distribution  $f$  of the variate is given by the multivariate hypergeometric distribution ✂ add refs:

$$p(f|n, F, N, I) = \binom{N}{n}^{-1} \prod \binom{NF}{nf}. \quad (11)$$

We want to infer the distribution  $F$  given the distribution  $f$  of a sample of size  $n := 6029$ . Using Bayes's theorem,

$$p(F|f, n, N, I) = \frac{p(f|n, F, N, I) p(F|N, I)}{\sum_F p(f|n, F, N, I) p(F|N, I)}. \quad (12)$$

We need to assess our initial probability  $I$  about  $F$ ,  $p(F|N, I)$ . As a first tentative let's assume that this probability is constant for all possible distributions  $F$ :

$$p(F|N, I) = \binom{N+D-1}{D-1}^{-1}. \quad (13)$$

Substituting this and (11) into Bayes's theorem (12) and simplifying we obtain ✂ add refs for summation formula

$$p(F|f, n, N, I) = \binom{N+D-1}{n+D-1}^{-1} \prod \binom{NF}{nf}. \quad (14)$$

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[Luca's memoranda:]

- Use of partial exchangeability *has to* distinguish also between men and women: see Gehrman et al. (2013 p. 327).
- This study could also be used to detect most relevant genes, by eliminating them in turn (and in pairs etc) and checking the ensuing predictions.
- Is it computationally possible to use a ‘nonparametric model’? It would avoid unwarranted assumptions and phenomena like over-training.

## Bibliography

- (‘de X’ is listed under D, ‘van X’ under V, and so on, regardless of national conventions.)
- Barwise, J., Etchemendy, J. (2003): *Language, Proof and Logic*. (CSLI, Stanford). Written in collaboration with Gerard Allwein, Dave Barker-Plummer, Albert Liu. First publ. 1999.
- Bernardo, J.-M., DeGroot, M. H., Lindley, D. V., Smith, A. F. M., eds. (1988): *Bayesian Statistics 3*. (Oxford University Press, Oxford).
- Broad, C. D. (1918): *On the relation between induction and probability*. – (Part I.) *Mind* 27<sup>108</sup>, 389–404. See also Broad (1920).
- (1920): *On the relation between induction and probability*. – (Part II.) *Mind* 29<sup>113</sup>, 11–45. See also Broad (1918).
- Bush, W. S., Moore, J. H. (2012): *Genome-wide association studies*. *PLoS Comput. Biol.* 8<sup>12</sup>, e1002822.
- Copi, I. M., Cohen, C., McMahon, K. (2014): *Introduction to Logic*, 14th ed. (Pearson, Harlow, UK). First publ. 1953.
- Cover, T. M., Thomas, J. A. (2006): *Elements of Information Theory*, 2nd ed. (Wiley, Hoboken, USA). First publ. 1991.
- Csiszár, I., Shields, P. C. (2004): *Information theory and statistics: a tutorial*. *Foundations and Trends in Communications and Information Theory* 1<sup>4</sup>, 417–528. <http://www.renyi.hu/~csiszar/>.
- de Finetti, B. (1931): *Probabilismo*. *Logos* 14, 163–219. Transl. as de Finetti (1989). See also Jeffrey (1989).
- (1937): *La prévision : ses lois logiques, ses sources subjectives*. *Ann. Inst. Henri Poincaré* 7<sup>1</sup>, 1–68. Transl. in Kyburg, Smokler (1980), pp. 53–118, by Henry E. Kyburg, Jr.
- (1938): *Sur la condition d’équivalence partielle*. In: *Colloque consacré à la théorie des probabilités. VI : Conceptions diverses*. Ed. by B. de Finetti, V. Glivenko, G. Neymann (Hermann, Paris), 5–18. Transl. in Jeffrey (1980), pp. 193–205, by P. Benacerraf and R. Jeffrey.
- (1989): *Probabilism: A critical essay on the theory of probability and on the value of science*. *Erkenntnis* 31<sup>2–3</sup>, 169–223. Transl. of de Finetti (1931) by Maria Concetta Di Maio, Maria Carla Galavotti, and Richard C. Jeffrey.



- Diaconis, P. (1988): *Recent progress on de Finetti's notions of exchangeability*. In: Bernardo, DeGroot, Lindley, Smith (1988), 111–125. With discussion by D. Blackwell, Simon French, and author's reply. <http://statweb.stanford.edu/~cgates/PERSI/year.html>, <https://statistics.stanford.edu/research/recent-progress-de-finettis-notions-exchangeability>.
- Diaconis, P., Freedman, D. (1980): *De Finetti's generalizations of exchangeability*. In: Jeffrey (1980), 233–249.
- Duhem, P. (1914): *La Théorie Physique : son objet – sa structure*, 2nd ed. (Marcel Rivière, Éditeur, Paris). [http://virtualbooks.terra.com.br/freebook/fran/la\\_theorie\\_physique.htm](http://virtualbooks.terra.com.br/freebook/fran/la_theorie_physique.htm). First publ. 1906. Transl. as Duhem (1991).
- (1991): *The Aim and Structure of Physical Theory*, Transl. of the 2nd ed. (Princeton University Press, Princeton). Transl. of Duhem (1914) by P. P. Wiener. First publ. in French 1906.
- Gehrman, P. R., Pfeiffenberger, C., Byrne, E. M. (2013): *The role of genes in the insomnia phenotype*. Sleep Med. Clin. 8<sup>3</sup>, 323–331.
- Harding, S. G., ed. (1976): *Can Theories Be Refuted?* (D. Reidel, Dordrecht).
- Heath, D., Sudderth, W. (1976): *De Finetti's theorem on exchangeable variables*. American Statistician 30<sup>4</sup>, 188–189.
- Jeffrey, R. (1989): *Reading Probabilismo*. Erkenntnis 31<sup>2–3</sup>, 225–237. See de Finetti (1931).
- Jeffrey, R. C., ed. (1980): *Studies in inductive logic and probability*. Vol. II. (University of California Press, Berkeley).
- Jeffreys, H. (1983): *Theory of Probability*, third ed. with corrections. (Oxford University Press, London). First publ. 1939.
- Koch, G., Spizzichino, F., eds. (1982): *Exchangeability in Probability and Statistics*. (North-Holland, Amsterdam).
- Kyburg Jr., H. E., Smokler, H. E., eds. (1980): *Studies in Subjective Probability*, 2nd ed. (Robert E. Krieger, Huntington, USA). First publ. 1964.
- Medawar, P. B. (1963): *Is the scientific paper a fraud?* Listener 70, 377–378.
- Poincaré, H. (1905): *Science and Hypothesis*. (Walter Scott, London). Transl. of Poincaré (1992) by W. J. Greenstreet; with a Preface by J. Larmor. First publ. 1902. Partly repr. in Poincaré (1958).
- (1958): *The Value of Science*. (Dover, New York). Authorized transl. with an introduction by G. B. Halsted. First publ. 1913.
- (1992): *La science et l'hypothèse*. (Éditions de la Bohème, Rueil-Malmaison, France). <http://gallica.bnf.fr/document?0=N026745>. First publ. 1902; transl. as Poincaré (1905).
- Pratt, J. W., Raiffa, H., Schlaifer, R. (1996): *Introduction to Statistical Decision Theory*, 2nd pr. (MIT Press, Cambridge, USA). First publ. 1995.
- Raiffa, H., Schlaifer, R. (2000): *Applied Statistical Decision Theory*, reprint. (Wiley, New York). First publ. 1961.
- Sox, H. C., Higgins, M. C., Owens, D. K. (2013): *Medical Decision Making*, 2nd ed. (Wiley, New York). First publ. 1988.
- Stephens, M., Balding, D. J. (2009): *Bayesian statistical methods for genetic association studies*. Nat. Rev. Genet. 10, 681–690.
- Stingo, F. C., Swartz, M. D., Vannucci, M. (2015): *A bayesian approach to identify genes and gene-level SNP aggregates in a genetic analysis of cancer data*. Stat. Interface 8<sup>2</sup>, 137–151.
- Sugden, R. A. (1982): *Exchangeability and survey sampling inference*. In: Koch, Spizzichino (1982), 321–330.
- (1993): *Partial exchangeability and survey sampling inference*. Biometrika 80<sup>2</sup>, 451–455.