

a primer on
BAYESIAN STATISTICS

in Health Economics and
Outcomes Research

BAYESIAN INITIATIVE IN HEALTH ECONOMICS
& OUTCOMES RESEARCH



Centre for Bayesian Statistics
in Health Economics

A Primer on Bayesian Statistics

Luce O'Hagan

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Outcomes Research

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The objective of the Bayesian Initiative in Health Economics & Outcomes Research ("The Bayesian Initiative") is to explore the extent to which formal Bayesian statistical analysis can and should be incorporated into the field of health economics and outcomes research for the purpose of assisting rational health care decision-making. The Bayesian Initiative is organized by scientific staff at MEDTAP® International, Inc., a firm specializing in health and economics outcomes research. www.bayesian-initiative.com.

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Preface and Brief History

Let me begin by saying that I was trained as a Bayesian in the 1970s and drifted away because we could not do the computations that made so much sense to do. Two decades later, in the 1990s, I found the Bayesians had made tremendous headway with Markov chain Monte Carlo (MCMC) computational methods, and at long last there was software available. Since then I've been excited about once again picking up the Bayesian tools and joining a vibrant and growing worldwide community of Bayesians making great headway on real life problems.

In regard to the tone of the Primer, to certain readers it may sound a bit strident – especially to those steeped in classical/frequentist statistics. This is the legacy of a very old debate and tends to surface when advocates of Bayesian statistics once again have the opportunity to present their views. Bayesians have felt for a very long time that the mathematics of probability and inference are clearly in their favor, only to be ignored by “mainstream” statistics. Naturally, this smarts a bit. However, times are changing and today we observe the beginnings of a convergence, with frequentists finding merit in the Bayesian goals and methods and Bayesians finding computational techniques that now allow us the opportunity to connect the methods with the demands of practical science.

Communicating the Bayesian view can be a frustrating task since

we believe that current practices are logically flawed, yet taught and taken as gospel by many. In truth, there is equal frustration among some frequentists who are convinced Bayesians are opening science to vagaries of subjectivity. Curiously, although the debate rages, there is no dispute about the correctness of the mathematics. The fundamental disagreement is about a single definition from which everything else flows.

Why does the age-old debate evoke such passions? In 1925, writing in the relatively new journal, *Biometrika*, Egon Pearson noted:

Both the supporters and detractors of what has been termed Bayes' Theorem have relied almost entirely on the logic of their argument; this has been so from the time when Price, communicating Bayes' notes to the Royal Society [in 1763], first dwelt on the definite rule by which a man fresh to this world ought to regulate his expectation of succeeding sunrises, up to recent days when Keynes [*A Treatise on Probability*, 1921] has argued that it is almost discreditable to base any reliance on so foolish a theorem. [Pearson (1925), p. 388]

It is notable that Pearson, who is later identified mainly with the frequentist school, particularly the Neyman-Pearson lemma, supports the Bayesian method's veracity in this paper.

An accessible overview of Bayesian philosophy and methods, often cited as a classic, is the review by Edwards, Lindman, and Savage (1963). It is worthwhile to quote their recounting of history:

Bayes' theorem is a simple and fundamental fact about probability that seems to have been clear to Thomas Bayes when he wrote his famous article ... , though he did not state it there explicitly. Bayesian statistics is so named for the rather inadequate reason that it has many more occasions to apply Bayes' theorem than classical statistics has. Thus from a very broad point of view, Bayesian statistics date back to at least 1763.

From a stricter point of view, Bayesian statistics might properly be said to have begun in 1959 with the publication of *Probability and Statistics*

for Business Decisions, by Robert Schlaiffer. This introductory text presented for the first time practical implementation of the key ideas of Bayesian statistics: that probability is orderly opinion, and that inference from data is nothing other than the revision of such opinion in the light of relevant new information. [Edwards, Lindman, Savage (1963) pp 519-520]

This passage has two important ideas. The first concerns the definition of “probability”. The second is that although the ideas behind Bayesian statistics are in the foundations of statistics as a science, Bayesian statistics came of age to facilitate decision-making.

Probability is the mathematics used to describe uncertainty. The dominant view of statistics today, termed in this Primer the “frequentist” view, defines the probability of an event as the limit of the relative frequency with which it occurs in series of suitably relevant observations in which it could occur; notably, this series may be entirely hypothetical. To the frequentist, the locus of the uncertainty is in the events. Strictly speaking, a frequentist only attempts to quantify “the probability of an event” as a characteristic of a set of similar events, which are at least in principle repeatable copies. A Bayesian regards each event as unique, one which will or will not occur. The Bayesian says the probability of the event is a number used to indicate the opinion of a relevant observer concerning whether the event will or will not occur on a particular observation. To the Bayesian, the locus of the uncertainty described by the probability is in the observer. So a Bayesian is perfectly willing to talk about the probability of a unique event. Serious readers can find a full mathematical and philosophical treatment of the various conceptions of probability in Kyburg & Smokler (1964).

It is unfortunate that these two definitions have come to be characterized by labels with surplus meaning. Frequentists talk about their probabilities as being “objective”; Bayesian probabilities are termed “subjective”. Because of the surplus meaning invested in these labels, they are perceived to be polar opposites. Subjectivity is thought to be an undesirable proper-

ty for a scientific process, and connotes arbitrariness and bias. The frequentist methods are said to be objective, therefore, thought not to be contaminated by arbitrariness, and thus more suitable for scientific and arm's-length inquiries.

Neither of these extremes characterizes either view very well. Sadly, the confusion brought by the labels has stirred unnecessary passions on both sides for nearly a century.

In the Bayesian view, there may be as many different probabilities of an event as there are observers. In a very fundamental sense this is why we have horse races. This multiplicity is unsettling to the frequentist, whose worldview dictates a unique probability tied to each event by (in principle) longrun repeated sampling. But the subjective view of probability does not mean that probability is arbitrary. Edwards, et al., have a very important adjective modifying “opinion”: *orderly*. The subjective probability of the Bayesian must be orderly in the specific sense that it follows all of the mathematical laws of probability calculation, and in particular it must be revised in light of new data in a very specific fashion dictated by Bayes' theorem. The theorem, tying together the two views of probability, states that in the circumstance that we have a long-run series of relevant observations of an event's occurrences and non-occurrences, no matter how spread out the opinions of multiple Bayesian observers are at the beginning of the series, they will update their opinions as each new observation is collected. After many observations their opinions will converge on nearly the same numerical value for the probability. Furthermore, since this is an event for which we can define a long-run sequence of observations, a lemma to the theorem says that the numerical value upon which they will converge in the limit is exactly the long-run relative frequency!

Thus, where there are plentiful observations, the Bayesian and the frequentist will tend to converge in the probabilities they assign to events. So what is the problem?

There are two. First, there are events—one might even say that most events of interest for real world decisions—for which we do not have

ample relevant data in just one experiment. In these cases, both Bayesians and frequentists will have to make subjective judgments about which data to pool and which not to pool. The Bayesian will tend to be inclusive, but weight data in the pooled analysis according to its perceived relevance to the estimate at hand. Different Bayesians may end at different probability estimates because they start from quite different prior opinions and the data do not outweigh the priors, and/or they may weight the pooled data differently because they judge the relevance differently. Frequentists will decide, subjectively since there are no purely objective criteria for “relevance”, which data are considered relevant and which are not and pool those deemed relevant with full weight given to included data. Frequentists who disagree about relevance of different pre-existing datasets will also disagree on the final probabilities they estimate for the events of interest. An outstanding example of this happened in 2002 in the high profile dispute over whether screening mammography decreases breast cancer mortality. That dispute is still is not settled.

The second problem is that Bayesians and frequentists disagree to what events it is appropriate and meaningful to assign probabilities. Bayesians compute the probability of a specific hypothesis given the observed data. Edwards, et al., start counting the Bayesian era from publication of a book about using statistics to make business decisions; the reason for this is that the probability that a particular event will obtain (or hypothesis is true), given the data, is exactly what is needed for making decisions that depend on that event (or hypothesis). Unfortunately, within the mathematics of probability this particular probability cannot be computed without reference to some prior probability of the event before the data were collected. And, including a prior probability brings in the topic of subjectivity of probability.

To avoid this dilemma, frequentists—particularly RA Fisher, J Neyman and E Pearson—worked to describe the strength of the evidence independent of the prior probabilities of hypotheses. Fisher invented the P-value, and Neyman and Pearson invented testing of the null hypothesis

using the P-value.

Goodman beautifully summarized the history and consequences of this in an exceptionally clearly written paper a few years ago (Goodman, 1999). A statistician using the Neyman & Pearson method and P-values to reject null hypotheses at the 5% level will, on average in the long run (say over the career of that statistician), only make the mistake of rejecting a true null hypothesis about 5% of the time. However, the computations say nothing about a specific instance with a specific set of data and a specific null hypothesis, which is a unique event and not a repeatable event. There is no way, using the data alone, to say how likely it is that the null hypothesis is true in a specific instance. At most the data can tell you how far you should move away from your prior probability that the hypothesis is true. A Bayesian can compute this probability because to a Bayesian it makes sense to state a prior probability of a unique event.

Actually, as further recounted by Goodman, Neyman & Pearson were smart and realized that hypothesis testing did not get them out of the bind – as did many other intelligent statisticians. One response in the community of frequentists was to move from hypothesis testing to interval estimation – estimation of so-called confidence intervals likely to contain the parameter value of interest upon which the hypothesis depends. Unfortunately, this did not solve the problem but sufficiently regressed it into deep mathematics as to obfuscate whether or not it was solved.

So what does all of this mean for someone who is trained in frequentist statistics or for someone who is wondering what Bayesian methods offer? Let us call this person “You”.

At the very least, it means You will discover a new way to compute intervals very close to those you get in computing traditional confidence intervals. Your only reward lies in the knowledge that the specific interval has the stated probability of containing the parameter, which is not the case with the nearly identical interval computed in the traditional manner. Admittedly, this does not seem like much gain.

It also means that You will have to think differently about the statisti-

cal problem You are solving, which will mean additional work. In particular, You may have to put real effort into specifying a prior probability that You can defend to others. While this may be uncomfortable Bayesians are working on ways to help You with both the process of understanding and specifying the prior probabilities as well as the arguments to defend them.

Here is what You will get in return. First, in any specific analysis for a specific dataset and specific hypothesis (not just the null hypothesis) You will be able to compute the probability that the hypothesis is true. Or, often more useful, You will be able to specify the probability that the true value of the parameter is within any given interval. This is what is needed for quantitative decision-making and for weighing the costs and benefits of decisions depending on these estimates.

Second, You will get an easy way to revise Your estimate in an orderly and defensible fashion as you collect new data relevant to Your problem.

The first two gains give You a third: this way of thinking and computing frees You from some of the concerns about peeking at Your data before the planned end of the trial. In fact, it gives You a whole new set of tools to dynamically optimize trial sizes with optional stopping rules. This is a very advanced topic in Bayesian methods – far beyond this Primer –but for which there is growing literature.

Yet another gain is that others who depend on Your published results to compute such things as a cost-effectiveness ratio can now directly incorporate uncertainty in a meaningful way to specify precision of their results. While this may be an indirect gain to You it gives added value to Your analyses.

A fifth gain, stemming from advances in computation methods stimulated by Bayesians' needs, is that you can naturally and easily estimate distributions for functions of parameters estimated in turn in quite complicated statistical models to represent the data generating processes. You will be freed from reliance on simplistic formulations of the data likelihood solely for the purpose of being able to use standard tests. In many ways this is analogous to the immense advances in our capability to estimate quite

sophisticated regression models over the simple linear models of yesterday.

Finally, You will not get left behind. There is a beginning sea change taking place in statistics and the ability to understand, apply and criticize a Bayesian analysis will be important to researchers and practitioners in the near future.

I hope You will find all these gains accruing to You as time marches forward. It will require investment in relearning some of the fundamentals with little apparent benefit at first. But if You persist, my probability is high that You will succeed.

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Overview

This Primer is for health economists, outcomes research practitioners and biostatisticians who wish to understand the basics of Bayesian statistics, and how Bayesian methods may be applied in the economic evaluation of health care technologies. It requires no previous knowledge of Bayesian statistics. The reader is assumed only to have a basic understanding of traditional non-Bayesian techniques, such as unbiased estimation, confidence intervals and significance tests; that traditional approach to statistics is called ‘frequentist’.

The Primer has been produced in response to the rapidly growing interest in, and acceptance of, Bayesian methods within the field of health economics. For instance, in the United Kingdom the National Institute for Clinical Excellence (NICE) specifically accepts Bayesian approaches in its guidance to sponsors on making submissions. In the United States the Food and Drug Administration (FDA) is also open to Bayesian submissions, particularly in the area of medical devices. This upsurge of interest in the Bayesian approach is far from unique to this field, though; we are seeing at the start of the 21st century an explosion of Bayesian methods throughout science, technology, social sciences, management and commerce. The reasons are not hard to find, and are similar in all areas of application. They are based on the following key **benefits** of the Bayesian approach:

- (B1) Bayesian methods provide more natural and useful inferences than frequentist methods.
- (B2) Bayesian methods can make use of more available information, and so typically produce stronger results than frequentist methods.
- (B3) Bayesian methods can address more complex problems than frequentist methods.
- (B4) Bayesian methods are ideal for problems of decision making, whereas frequentist methods are limited to statistical analyses that inform decisions only indirectly.
- (B5) Bayesian methods are more transparent than frequentist methods about all the judgements necessary to make inferences.

We shall see how these benefits arise, and their implications for health economics and outcomes research, in the remainder of this Primer. However, even a cursory look at the benefits may make the reader wonder why frequentist methods are still used at all. The answer is that there are also widely perceived **drawbacks** to the Bayesian approach:

- (D1) Bayesian methods involve an element of subjectivity that is not overtly present in frequentist methods.
- (D2) In practice, the extra information that Bayesian methods utilize is difficult to specify reliably.
- (D3) Bayesian methods are more complex than frequentist methods, and software to implement them is scarce or non-existent.

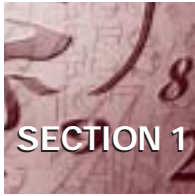
The authors of this Primer are firmly committed to the Bayesian approach, and believe that the drawbacks can be, are being and will be overcome. We will explain why we believe this, but will strive to be honest about the competing arguments and the current state of the art.

This Primer begins with a general discussion of the benefits and drawbacks of Bayesian methods versus the frequentist approach, including an explanation of the basic concepts and tools of Bayesian statistics. This part comprises five sections, entitled *Inference*, *The Bayesian Method*, *Prior Information*, *Prior Specification* and *Computation*, which present all of the key facts and arguments regarding the use of Bayesian statistics in a simple, non-technical way.

The level of detail given in these sections will, hopefully, meet the needs of many readers, but deeper understanding and justification of the claims made in the main text can also be found in the Appendix. We stress that the Appendix is still addressed to the general reader, and is intended to be non-technical.

The last two sections, entitled *Design and Analysis of Trials and Economic Models*, provide illustrations of how Bayesian statistics is already contributing to the practice of health economics and outcomes research. We should emphasize that this is a fast-moving research area, and these sections may go out of date quickly. We hope that readers will be stimulated to play their part in these exciting developments, either by devising new techniques or by employing existing ones in their own applications.

Finally, the *Conclusions* section summarizes the arguments in this Primer, and a *Further Reading* list provides some general suggestions for further study of Bayesian methods and their application in health economics.



SECTION 1

Inference

In order to obtain a clear understanding of the benefits and drawbacks to the Bayesian approach, we first need to understand the basic differences between Bayesian and frequentist inference. This section addresses the nature of probability, parameters and inferences under the two approaches.

Frequentist and Bayesian methods are founded on different notions of probability. According to frequentist theory, only repeatable events have probabilities. In the Bayesian framework, probability simply describes uncertainty. The term “uncertainty” is to be interpreted in its widest sense. An event can be uncertain by virtue of being intrinsically unpredictable, because it is subject to random variability, for example the response of a randomly selected patient to a drug. It can also be uncertain simply because we have imperfect knowledge of it, for example the mean response to the drug across all patients in the population. Only the first kind of uncertainty is acknowledged in frequentist statistics, whereas the Bayesian approach encompasses both kinds of uncertainty equally well.

Example.

Suppose that Mary has tossed a coin and knows the outcome, Heads or Tails, but has not revealed it to Jamal. What probability should Jamal give to it being Head? When asked this question,

most people say that the chances are 50-50, i.e. that the probability is one-half. This accords with the Bayesian view of probability, in which the outcome of the toss is uncertain for Jamal so he can legitimately express that uncertainty by a probability. From the frequentist perspective, however, the coin is either Head or Tail and is not a random event. For the frequentist it is no more meaningful for Jamal to give the event a probability than for Mary, who knows the outcome and is not uncertain. The Bayesian approach clearly distinguishes between Mary's and Jamal's knowledge.

Statistical methods are generally formulated as making *inferences* about unknown *parameters*. The parameters represent things that are unknown, and can usually be thought of as properties of the *population* from which the data arise. Any question of interest can then be expressed as a question about the unknown values of these parameters. The reason why the difference between the frequentist and Bayesian notions of probability is so important is that it has a fundamental implication for how we think about parameters. Parameters are specific to the problem, and are not generally subject to random variability. Therefore, frequentist statistics does not recognize parameters as being random and so does not regard probability statements about them as meaningful. In contrast, from the Bayesian perspective it is perfectly legitimate to make probability statements about parameters, simply because they are unknown.

Note that in Bayesian statistics, as a matter of convenient terminology, we refer to any uncertain quantity as a random variable, even when its uncertainty is not due to randomness but to imperfect knowledge.

Example.

Consider the proposition that treatment 2 will be more cost-effective than treatment 1 for a health care provider. This proposition concerns unknown parameters, such as each treatment's mean cost and mean efficacy across all patients in the population for which the health care

provider is responsible. From the Bayesian perspective, since we are uncertain about whether this proposition is true, the uncertainty is described by a probability. Indeed, the result of a Bayesian analysis of the question can be simply to calculate the probability that treatment 2 is more cost-effective than treatment 1 for this health care provider. From the frequentist perspective, however, whether treatment 2 is more cost-effective is a one-off proposition referring to two specific treatments in a specific context. It is not repeatable and so we cannot talk about its probability.

In this last example, the frequentist can conduct a significance test of the null hypothesis that treatment 2 is not more cost-effective, and thereby obtain a P-value. At this point, the reader should examine carefully the statements in the box “Interpreting a P-value” below, and decide which ones are correct.

Interpreting a P-value

The null hypothesis that treatment 2 is not more cost-effective than treatment 1 is rejected at the 5% level, i.e. $P = 0.05$. What does this mean?

1. Only 5% of patients would be more cost-effectively treated by treatment 1.
2. If we were to repeat the analysis many times, using new data each time, and if the null hypothesis were really true, then on only 5% of those occasions would we (falsely) reject it.
3. There is only a 5% chance that the null hypothesis is true.

Statement 3 is how a P-value is commonly interpreted; yet this interpretation is not correct because it makes a probability statement about the hypothesis, which is a Bayesian, not a frequentist, concept. The correct interpretation of the P-value is much more tortuous and is given by Statement 2. (Statement 1 is another fairly common misinterpretation. Since the hypothesis is about mean cost and mean efficacies, it says noth-

ing about individual patients.)

The primary reason why we cannot interpret a P-value in this way is because it does not take account of how plausible the null hypothesis was *a priori*.

Example.

An experiment is conducted to see whether thoughts can be transmitted from one subject to another. Subject A is presented with a shuffled deck of cards and tries to communicate to Subject B whether each card is red or black by thought alone. In the experiment, Subject B correctly gives the color of 33 cards. The null hypothesis is that no thought-transference takes place and Subject B is randomly guessing. The observation of 33 correct is significant with a (one-sided) P-value of 3.5%. Should we now believe that it is 96.5% certain that Subject A can transmit her thoughts to Subject B?

Most scientists would regard thought-transference as highly implausible and in no way would be persuaded by a single, rather small, experiment of this kind. After seeing this experimental result, most would still strongly believe in the null hypothesis, regarding the outcome as due to chance.

In practice, frequentist statisticians recognize that much stronger evidence would be required to reject a highly plausible null hypothesis, such as in the above example, than to reject a more doubtful null hypothesis. This makes it clear that the P-value cannot mean the same thing in all situations and to interpret it as the probability of the null hypothesis is not only wrong but could be seriously wrong when the hypothesis is a *priori* highly plausible (or highly implausible).

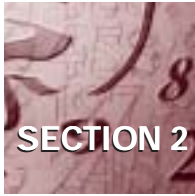
To many users of statistics and even to many practicing statisticians, it is perplexing that one cannot interpret a P-value as the probability that the null hypothesis is true. Similarly, it is perplexing that one cannot interpret

a 95% confidence interval for a treatment difference as saying that the true difference has a 95% chance of lying in this interval. Nevertheless, these are wrong interpretations...and can be seriously wrong. The correct interpretations are far more indirect and unintuitive. (See the Appendix for more examples.)

Bayesian inferences have exactly the desired interpretations. A Bayesian analysis of a hypothesis results precisely in the probability that it is true. In addition, a Bayesian 95% interval for a parameter means precisely that there is a 95% probability that the parameter lies in that interval. This is the essence of the key benefit (B1) – “more natural and interpretable inferences” – offered by Bayesian methods.

TABLE 1. Summary of Key Differences Between Frequentist and Bayesian Approaches

FREQUENTIST	BAYESIAN
<i>Nature of probability</i>	
Probability is a limiting, long-run frequency.	Probability measures a personal degree of belief.
It only applies to events that are (at least in principle) repeatable.	It applies to any event or proposition about which we are uncertain.
<i>Nature of parameters</i>	
Parameters are not repeatable or random.	Parameters are unknown.
They are therefore not random variables, but fixed (unknown) quantities.	They are therefore random variables.
<i>Nature of inference</i>	
Does not (although it appears to) make statements about parameters.	Makes direct probability statements about parameters.
Interpreted in terms of long-run repetition.	Interpreted in terms of evidence from the observed data.
<i>Example</i>	
"We reject this hypothesis at the 5% level of significance."	"The probability that this hypothesis is true is 0.05."
In 5% of samples where the hypothesis is true it will be rejected (but nothing is stated about this sample).	The statement applies on the basis of <i>this</i> sample (as a degree of belief).



SECTION 2

The Bayesian Method

The fundamentals of Bayesian statistics are very simple. The Bayesian paradigm is one of learning from data.

The role of data is to add to our knowledge and so to update what we can say about the parameters and relevant hypotheses. As such, whenever we wish to learn from a new set of data, we need to identify what is known *prior* to observing those data. This is known as prior information. It is through the incorporation of prior information that the Bayesian approach utilizes more information than the frequentist approach. A discussion of precisely what the prior information represents and where it comes from can be found in the next section: *Prior Information*. For purposes of exposition of how the Bayesian paradigm works, we simply suppose that the prior information has been identified and is expressed in the form of a **prior distribution** for the unknown parameters of the statistical model. The prior distribution expresses what is known (or believed to be true) before seeing the new data. This information is then synthesized with the information in the data to produce the **posterior distribution**, which expresses what we now know about the parameters after seeing the data. (We often refer to these distributions as ‘the prior’ and ‘the posterior’.)

The mathematical mechanism for this synthesis is **Bayes’ theorem**, and this is why this approach to statistics is called “Bayesian”. From a historical perspective, the name originated from the Reverend

Thomas Bayes, an 18th century minister who first showed the use of the theorem in this way and gave rise to Bayesian statistics.

The process is simply illustrated in the box “Example of Bayes’ theorem”.

Figure 1 is called a **triplot** and is a way of seeing how Bayesian methods combine the two information sources. The strength of each source of information is indicated by the narrowness of its curve – a narrower curve rules out more parameter values and so represents stronger information. In Figure 1, we see that the new data (red curve) are a little more informative than the prior (grey curve). Since Bayes’ theorem recognizes the strength of each source, the posterior (black dotted curve) in Figure 1 is influenced a little more by the data than by the prior. For instance, the posterior peaks at 1.33, a little closer to the peak of the data curve than to the prior peak. Notice that the posterior is narrower than either the prior or the data curve, reflecting the way that the posterior has drawn strength from both information sources.

The data curve is technically called the likelihood and is also important in frequentist inference. Its role in both inference paradigms is to describe the strength of support from the data for the various possible values of the parameter. The most obvious difference between frequentist and Bayesian methods is that frequentist statistics uses only the likelihood, whereas Bayesian statistics uses both the likelihood and the prior information.

In Figure 1, the Bayesian analysis produces different inferences from the frequentist approach because it uses the prior information as well as the data. The frequentist estimate, using the data alone, is around 1.5. The Bayesian analysis uses the fact that it is unlikely, on the basis of the prior information, that the true parameter value is 2 or more. As a result, the Bayesian estimate is around 1. The Bayesian analysis combines the prior information and data information in a similar way to how a meta-analysis combines information from several reported trials. The posterior estimate is a compromise between prior and data estimates and is a more precise estimate (as seen in the posterior density being a narrower curve) than

Example of Bayes' Theorem

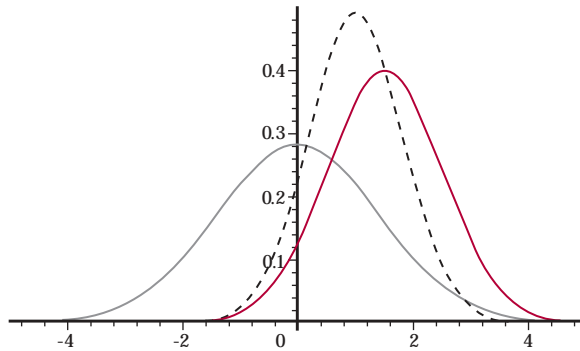


Figure 1. The prior distribution (grey) and information from the new data (red) are synthesized to produce the posterior distribution (black dotted).

In this example, the prior information (grey curve) tells us that the parameter is almost certain to lie between -4 and $+4$, that it is most likely to be between -2 and $+2$, and that our best estimate of it would be 0 .

The data (red curve) favor values of the parameter between 0 and 3 , and strongly argue against any value below -2 .

The posterior (black dotted curve) puts these two sources of information together. So, for values below -2 the posterior density is tiny because the data are saying that these values are highly implausible. Values above $+4$ are ruled out by the prior; again, the posterior agrees. The data favors values around 1.5 , while the prior prefers values around 0 . The posterior listens to both and the synthesis is a compromise. After seeing the data, we now think the parameter is most likely to be around 1 .

either information source separately. This is the key benefit (B2) – “ability to make use of more information and to obtain stronger results” – that the Bayesian approach offers.

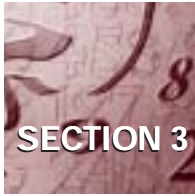
According to the Bayesian paradigm, any inference we desire is derived from the posterior distribution. One estimate of a parameter might be the mode of this distribution (i.e. the point where it reaches its maximum). Another common choice of estimate is the posterior expectation. If we have a hypothesis, then the probability that the hypothesis is true is also derived from the posterior distribution. For instance, in Figure 1 the

probability that the parameter is positive is the area under the black dotted curve to the right of the origin, which is 0.89.

In contrast to frequentist inference, which must phrase all questions in terms of significance tests, confidence intervals and unbiased estimators, Bayesian inference can use the posterior distribution very flexibly to provide relevant and direct answers to all kinds of questions. One example is the natural link between Bayesian statistics and decision theory. By combining the posterior distribution with a utility function (which measures the consequences of different decisions), we can identify the optimal decision as that which maximizes the expected utility. In economic evaluation, this could reduce to minimizing expected cost or to maximizing expected efficacy, depending on the utility function. However, from the perspective of cost-effectiveness, the most appropriate utility measure is net benefit (defined as the mean efficacy times willingness to pay, minus expected cost).

For example, consider a health care provider that has to choose which of two procedures to reimburse. The optimal decision is to choose the one that has the higher *expected* net benefit. A Bayesian analysis readily provides this answer, but there is no analogous frequentist analysis. To test the hypothesis that one net benefit is higher than the other simply does not address the question properly (in the same way that to compute the probability that the net benefit of procedure 2 is higher than that of procedure 1 is not the appropriate Bayesian answer). More details of this example and of Bayes' theorem can be found in the Appendix.

This serves to illustrate another key benefit of Bayesian statistics, (B4) – “Bayesian methods are ideal for decision making”.



SECTION 3

Prior Information

The prior information is both a strength and a potential weakness of the Bayesian approach. We have seen how it allows Bayesian methods to access more information and so to produce stronger inferences. As such it is one of the key benefits of the Bayesian approach. On the other hand, most of the criticism of Bayesian analysis focuses on the prior information.

The most fundamental criticism is that prior information is subjective: your prior information is different from mine, and so my prior distribution is different from yours. This makes the posterior distribution, and all inferences derived from it, subjective. In this sense, it is claimed that the whole Bayesian approach is subjective. Indeed, Bayesian methods are based on a subjective interpretation of probability, which is described in Table 1 as a “personal degree of belief”. This formulation is necessary (see the Appendix for details) if we are to give probabilities to parameters and hypotheses, since the frequentist interpretation of probability is too narrow. Yet for many scientists trained to reject subjectivity whenever possible, this is too high a price to pay for the benefits of Bayesian methods. To its critics, (D1) “subjectivity” is the key drawback of the Bayesian approach.

We believe that this objection is unwarranted both in principle and in practice. It is unwarranted in principle because science cannot be truly objective. In practice it is unwarranted because the Bayesian

method actually very closely reflects the real nature of the scientific method, in the following respects:

Subjectivity in the prior distribution is minimized through basing prior information on defensible evidence and reasoning.

Through the accumulation of data, differences in prior positions are resolved and consensus is reached.

Taking the second of these points first, Bayes' theorem weights the prior information and data according to their relative strengths in order to derive the posterior distribution. If prior information is vague and insubstantial then it will get negligible weight in the synthesis with the data, and the posterior will in effect be based entirely on data information (as expressed in the likelihood function). Similarly, as we acquire more and more data, the weight that Bayes' theorem attaches to the newly acquired data relative to the prior increases. Again, the posterior is effectively based entirely on the information in the data. This feature of Bayes' theorem mirrors the process of science, where the accumulation of objective evidence is the primary process whereby differences of opinion are resolved. Once the data provide conclusive evidence, there is essentially no room left for subjective opinion.

Returning to the first point above, it is stated that where genuine, substantial prior information exists it needs to be based on defensible evidence and reasoning. This is clearly important when the new data are not so extensive as to overwhelm the prior information, so that Bayes' theorem will give the prior a non-negligible weight in its synthesis with the data. Prior information of this kind exists routinely in medical applications, and in particular in economic evaluation of competing technologies.

Two examples are presented in the Appendix. One concerns the analysis of subgroup differences, where prior skepticism about the existence of such effects without a plausible biological mechanism is naturally accommodated in the Bayesian analysis.

The other example concerns a case where a decision on the cost-effectiveness of a new drug versus standard treatment depends in large part on evidence about hospitalizations. A small trial produces an apparently large

(and, in frequentist terms, significant) reduction in mean days in hospital. However, an earlier and much larger trial produced a much less favorable estimate of mean hospital days for a similar drug. There are two possible responses that a frequentist analysis can have to the earlier trial:

1. Take the view that there is no reason why the hospitalization rate under the old drug should be the same as under the new one, in which case the earlier trial is ignored because it contributes no information about the new drug.
2. Take the view that the two drugs should have essentially identical hospitalization rates – and so we pool the data from the two trials.

The second option will lead to the new data being swamped by the much larger earlier trial, which seems unreasonable, but the first option entails throwing away potentially useful information. In practice, a frequentist would probably take the first option, but with a caveat that the earlier trial suggests this may underestimate the true rate.

It would usually be more realistic to take the view that the two hospitalization rates will be *different but similar*. The Appendix demonstrates how a Bayesian analysis can accommodate the earlier trial as prior information although it necessitates a judgement about similarity of the drugs. How different might we have believed their hospitalization rates to be before conducting the new trial?

The Bayesian analysis produces a definite and quantitative synthesis of the two sources of information rather than just the vague “an earlier trial on a similar drug produced a higher mean days in hospital, and so I am skeptical about the reduction seen in this trial”. This synthesis results from making a clear, reasoned and transparent interpretation of the prior information. This is part of the key benefit (B5) – “more transparent judgements” – of the Bayesian approach. Without the Bayesian analysis it would be natural to moderate the claims of the new trial. The extent of such moderation would still be judgmental, but the judgement would not be so open and the result would not be transparently derived from the judgement by Bayes’ theorem.

This leads to another important way in which Bayesian methods are transparent. Once the prior distribution and likelihood have been formulated (and openly laid on the table), the computation of the posterior distribution and the derivation of appropriate posterior inferences or decisions are uniquely determined. In contrast, once the likelihood has been determined in a frequentist analysis there is still the freedom to choose which of many inference rules to apply. For instance, although in simple problems it is possible to identify optimal estimators, in general, there are likely to be many unbiased estimators – none of which dominates any of the others in the sense of having uniformly smaller variance. The practitioner is then free to use any of these or to dream up others on an “ad hoc” basis. This feature of frequentism leads to a lack of transparency because the respective choices are, in essence, arbitrary.

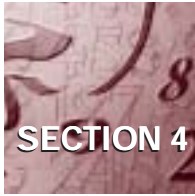
So what of the criticism (D1), that Bayesian methods are inherently subjective? It is true that one could carry out a Bayesian analysis with a prior distribution based on mere guesswork, prejudice or wishful thinking. Bayes’ theorem technically admits all of these unfortunate practices, but Bayesian statistics does not in any sense condone them. Also, recall that in a proper Bayesian analysis, prior information is not only transparent but is also based on both defensible evidence and reasoning which, if followed, will lead any above-mentioned abuses to become transparent, and so to be rejected.

A compact statement of what should constitute prior information is provided in the box ‘The Evidence’.

The ‘Evidence’

Prior information should be based on sound evidence and reasoned judgements. A good way to think of this is to parody a familiar quotation: the prior distribution should be **‘the evidence, the whole evidence and nothing but the evidence’**:

- ‘the evidence’ – genuine information legitimately interpreted;
- ‘the whole evidence’ – not omitting relevant information (preferably a consensus that pools the knowledge of a range of experts);
- ‘nothing but the evidence’ – not contaminated by bias or prejudice.



SECTION 4

Prior Specification

We hope that the preceding sections convince the reader that prior information exists and should be used, in as reasoned, objective and fully transparent a way as possible. Here we address the question of how to formulate a prior probability distribution, the grey curve in Figure 1.

Refer to the example in the previous section where prior information consists of information about hospitalization in a trial of a similar drug. In the Appendix this is formulated as a prior distribution with mean 0.21 (average days in hospital per patient) and standard deviation 0.08. This is justified by reference to the trial in question, where the average days in hospital under the different but similar drug was estimated to be 0.21 with a standard error of 0.03. But how is the stated prior distribution obtained from the given prior information?

Judgement inevitably intervenes in the process of specifying the prior distribution. As in the above case, it typically arises through the need to interpret the prior information and its relevance to the new data. How different might the hospitalization rates be under the two drugs? Different experts may interpret the prior information differently. As well, a given expert may interpret the information differently at a later time, such as in the example of deciding on a prior standard deviation of 0.75 rather than 0.8.

Even though our prior information might be genuine evidence with a clear relation to the new data, we cannot convert this into a prior distribution with perfect precision and reliability. This is the drawback (D2) – “prior specification is unreliable”.

Nevertheless, in practice we only need to specify the prior distribution with **sufficient** reliability and accuracy. We can explore the range of plausible prior specifications based on reasonable interpretations of the evidence and allowing for imprecision in the necessary judgements. If the posterior inferences or decisions are essentially insensitive to those variations, then the inherent unreliability of the prior specification process does not matter. This practice of **sensitivity analysis** with respect to the prior specification is a basic feature of practical Bayesian methodology as it is in all decision analysis applications.

Types and definitions of prior distribution

Informative (or genuine) priors: represent genuine prior information and best judgement of its strength and relation to the new data.

Noninformative (or default, reference, improper, weak, ignorance) priors: represent complete lack of credible prior information.

Skeptical priors: supposed to represent a position that a null hypothesis is likely to be true.

Structural (or hierarchical) priors: incorporate genuine prior information about relationships between parameters.

The precision needed in the prior specification to achieve robust inferences and decisions depends on the strength of the new data. As we have seen, given strong enough data, the prior information matters little or not at all and differences of judgement in interpreting the data will be unimportant. When the new data are not so strong, and prior information is appreciable, then sensitivity analysis is essential. It is also important to note that, despite obvious drawbacks, expert opinion is sometimes quite a use-

ful component of prior information. The procedures to elicit expert judgments are an active topic of research by both statisticians and psychologists.

Up until now, we have been considering genuine informative prior distributions. Some other ways to specify the prior distribution in a Bayesian analysis are set out in the box, “Types and definitions of prior distribution”.

In response to the difficulty of accurately and reliably eliciting prior distributions, some have proposed conventional solutions that are supposed to represent either no prior beliefs or a skeptical prior position.

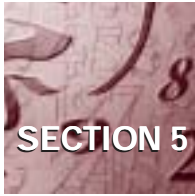
The argument in favor of representing no prior information is that this avoids any criticism about subjectivity. There have been numerous attempts to find a formula for representing prior ignorance, but without any consensus. Indeed, it is almost certainly an impossible quest. Nevertheless, the various representations that have been derived can be useful – at least for representing relatively *weak* prior information.

When the new data are strong (relative to the prior information), the prior information is not expected to make any appreciable contribution to the posterior. In this situation, it is pointless (and not cost-effective) to spend much effort on carefully eliciting the available prior information. Instead, it is common in such a case to apply some conventional ‘non-informative’, ‘default’, ‘reference’, ‘improper’, ‘vague’, ‘weak’ or ‘ignorance’ prior (although the last of these is really a misnomer). These terms are used more or less interchangeably in Bayesian statistics to denote a prior distribution representing very weak prior information. The term ‘improper’ is used because technically most of these distributions do not actually exist in the sense that a normal distribution with an infinite variance does not exist.

The idea of using so-called ‘skeptical’ priors is that if a skeptic can be persuaded by the data then anyone with a less skeptical prior position would also be persuaded. Thus, if one begins with a skeptical prior position with regard to some hypothesis and is nevertheless persuaded by the data, so that their posterior probability for that hypothesis is high, then some-

one else with a less skeptical prior position would end up giving that hypothesis an even higher posterior probability. In that case, the data are strong enough to reach a firm conclusion. If, on the other hand, when we use a skeptical prior the data are not strong enough to yield a high posterior probability for that hypothesis, then we should not yet claim any definite inference about it. Although this is another tempting idea, there is even less agreement or understanding about what a skeptical prior should look like.

The rather more complex ideas of structural or hierarchical priors (the last category in the box “Types and definitions of prior distribution”) are discussed in the Appendix.



SECTION 5

Computation

Software is essential for any but the simplest of statistical techniques, and Bayesian methods are no exception. In Bayesian statistics, the key operations are to implement Bayes' theorem and then to derive relevant inferences or decisions from the posterior distribution. In very simple problems these tasks can be done algebraically, but this is not possible in even moderately complex problems.

Until the 1990s, Bayesian methods were interesting, but they found little practical application because the necessary computational tools and software had not been developed. Anyone who wanted to do serious statistical analysis had no alternative but to use frequentist methods. In little over a decade that position has been dramatically turned around. Computing tools were developed specifically for Bayesian analysis that are more powerful than anything available for frequentist methods in the sense that Bayesians can now tackle enormously intricate problems that frequentist methods cannot begin to address. It is still true that Bayesian methods are more complex and that, although the computational techniques are well understood in academic circles, there is still a lack of user-friendly software for the general practitioner.

The transformation is continuing, and computational developments are shifting the balance between the drawback (D3) – “complexity and lack of software” – and the benefit (B3) – “ability to tackle more complex problems”. The main tool is a simulation technique

called *Markov chain Monte Carlo* (MCMC). The idea of MCMC is in a sense to bypass the mathematical operations rather than to implement them. Bayesian inference is solved by randomly drawing a very large simulated sample from the posterior distribution. The point is that if we have a sufficiently large sample from any distribution then we effectively have that whole distribution in front of us. Anything we want to know about the distribution we can calculate from the sample. For instance, if we wish to know the posterior mean we just calculate the mean of this 'inferential sample'. If the sample is big enough, the sample mean is an extremely accurate approximation to the true distribution mean, such that we can ignore any discrepancy between the two.

The availability of computational techniques like MCMC makes exact Bayesian inferences possible even in very complex models. Generalized linear models, for example, can be analyzed exactly by Bayesian methods, whereas frequentist methods rely on approximations. In fact, Bayesian modelling in seriously complex problems freely combines components of different sorts of modelling approaches with structural prior information, unconstrained by whether such model combinations have ever been studied or analyzed before. The statistician is free to model the data and other available information in whatever way seems most realistic. No matter how messy the resulting model, the posterior inferences can be computed (in principle, at least) by MCMC.

Bayesian methods have become the only feasible tools in several fields such as image analysis, spatial epidemiology and genetic pedigree analysis.

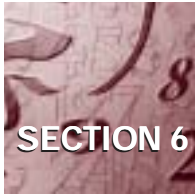
Although there is a growing range of software available to assist with Bayesian analysis, much of it is still quite specialized and not very useful for the average analyst. Unfortunately, there is nothing available yet that is both powerful and user-friendly in the way that most people expect statistical packages to be. Two software packages that are in general use, freely

available and worth mentioning are *First Bayes* and *WinBUGS*.

First Bayes is a very simple program that is aimed at helping the beginner learn and understand how Bayesian methods work. It is not intended for serious analysis of data, nor does it claim to teach Bayesian statistics, but it is in use in several universities worldwide to support courses in Bayesian statistics. *First Bayes* can be very useful in conjunction with a textbook – such as those recommended in the *Further Reading* section of this Primer – and can be freely downloaded from <http://www.shef.ac.uk/~st1ao/>.

WinBUGS is a powerful program for carrying out MCMC computations and is in widespread use for serious Bayesian analysis. *WinBUGS* has been a major contributing factor to the growth of Bayesian applications and can be freely downloaded from <http://www.mrc-bsu.cam.ac.uk/bugs/>. Please note, however, that *WinBUGS* is currently not very user-friendly and sometimes crashes with inexplicable error messages. Given the growing popularity of Bayesian methods, it is likely that more robust, user-friendly commercial software will emerge in the coming years.

The Appendix provides more detail on these two sides of the Bayesian computing coin: the drawback (D3) – “complexity and lack of software” – and the benefit (B3) – “ability to tackle more complex problems”.



SECTION 6

Design and Analysis of Trials

Bayesian techniques are inherently useful for designing clinical trials because trials tend to be sequential, each designed based in large part on prior trial evidence. The substantial literature that is available regarding clinical trial design using Bayesian techniques is, of course, applicable to design of cost-effectiveness trials.

By their nature, cost-effectiveness trials always have prior clinical and probably some form of economic information, which in the frequentist approach would be used to set the power requirements for the trial, and hence to identify the sample size. Since the prior information is explicitly stated in Bayesian design techniques, the dependence of the chosen design on prior information is fully transparent. A Bayesian analysis would formulate prior knowledge about how large an effect might be achieved. For instance, in planning a Phase III trial there will be information from Phase II studies on which to base a prior distribution for the effect. This permits an informative approach to setting sample size.

For a given sample size, the Bayesian calculation computes the probability that the trial will successfully demonstrate a positive effect (see O'Hagan and Stevens, 2001b). This can then be directly linked to a decision about whether a trial of a certain size (and hence cost), with this assurance of success (and consequent financial return), is worth-

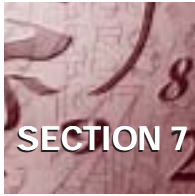
while. This contrasts with the frequentist power calculations, which only provide a probability of demonstrating an effect *conditional* on the unknown true effect taking some specific value.

An important simplifying feature of Bayesian design is that interim analyses can be introduced without affecting the final conclusions, and they do not need to be planned in advance. This is because Bayesian analysis does not suffer from the paradox of frequentist interim analysis, that two sponsors running identical trials and obtaining identical results may reach different conclusions if one performs an interim analysis (but does not stop the trial then) and the other does not. A Bayesian trial can be stopped early or extended for any appropriate reason without needing to compensate for such actions in subsequent analysis.

Aside from designing trials, a Bayesian approach is also useful for analyzing trial results. Today we see a growing interest in economic evaluation that has led to inclusion of cost-effectiveness as a secondary objective in traditional clinical trials. This may simply mean the collection of some resource use data alongside conventional efficacy trials, but may extend to more comprehensive economic data, more pragmatic enrollment, more relevant outcome measures and/or utilities. Methods of statistical analysis have begun to be developed for such trials. A useful review of Bayesian work in this area is O'Hagan and Stevens (2002).

Early statistical work concentrated on deriving inference for the incremental cost-effectiveness ratio, but the peculiar properties of ratios resulted in less than optimal solutions for various reasons. More recently, interest has focused on inference for the (incremental) net benefit, which is more straightforward statistically. Bayesian analyses have almost exclusively adopted the net benefit approach. In fact, when using net benefits the most natural expression of the relative cost-effectiveness of two treatments is the cost-effectiveness acceptability curve (van Hout et al, 1994); the essentially Bayesian nature of this measure is discussed in the Appendix.

Costs in trials, as everywhere, are invariably highly skewed. Bayesian methods accommodate this feature easily. O'Hagan and Stevens (2001a) provide a good example where the efficacy outcome is binary. They model costs as lognormally distributed (so explicitly accommodating skewness) and allow different lognormal distributions for patients who have positive or negative efficacy outcomes in each treatment group. They also illustrate how even simple structural prior information can help provide more realistic posterior inferences in a dataset where two very high cost patients arise in one patient group. Such a model is straightforwardly analyzed by MCMC. Stevens et al (2003) provide full details of *WinBUGS* code to compute posterior inferences. Another good example is Sutton et al (2003).



SECTION 7

Economic Models

Economic evaluation is widely practiced by building economic models (Chilcott et al, 2003). Even when cost-related data have been collected alongside efficacy in a clinical trial, they will rarely be adequate for a proper economic evaluation. This is because, as is widely understood, practice patterns within clinical trials differ radically from practice patterns in community medicine (the latter being the context of practical interest). More realistically, such data will inform some of the inputs (e.g. clinical efficacy data) to the cost-effectiveness model, while other input values (e.g. resource use, prices) will be derived from other sources.

Inputs to economic models can at best only be estimates of the unknown true values of these parameters – a fact that is recognized in the practice of performing sensitivity analysis. Often, this consists of a perfunctory one-way sensitivity analysis in which one input at a time is varied to some ad hoc alternative value and the model rerun to see if the cost-effectiveness conclusion changes. Even when none of these changes in single parameter values is enough to change the conclusion as to which treatment is more cost-effective, the analysis gives no quantification of the confidence we can attach to this being the correct inference. The true values of individual inputs might be outside the ranges explored. Furthermore, if two or more inputs are varied together within those ranges they might change the conclusion.

The statistically sound way to assess the uncertainty in the model output that arises from uncertainty in its inputs is probabilistic sensitivity analysis (PSA). This is the approach that is recommended by NICE, other statutory agencies and many academic texts. It consists of assigning probability distributions to the inputs, so as to represent the uncertainty we have in their true values, and then propagating this uncertainty through the model. There is increasing awareness of the benefits of PSA; two examples are Briggs et al (2002) and Parmigiani (2002).

It is important to appreciate that in PSA we are putting probability distributions on unknown parameters, which makes it unequivocally a Bayesian analysis. In effect, Bayesian methods have been widely used in health economics for years. The recognition of the Bayesian nature of these probability distributions has important consequences. The distributions should be specified using the ideas discussed in Section 4, *Prior Specification*. In particular, the evidence sought to populate economic models rarely relates directly to the parameters that the model actually requires in any application. Trial data will be from a different population (possibly in a different country) and with different compliance, registry data are potentially biased and so forth. Just as we considered with the use of prior information in general Bayesian analyses, the relationship between the data used to populate the model and the parameters that define the use we wish to make of the model is a matter for judgement. It is common to ignore these differences. However, using the estimates and standard errors reported in the literature as defining the input distributions will under-represent the true uncertainty.

The usual technique for PSA is Monte Carlo simulation, in which random sets of input values are drawn and the model run for each set. This gives a sample from the output distribution (which is very similar to MCMC sampling from the posterior distribution). This is feasible when the model is simple enough to run almost instantaneously on a computer but for more complex models it may be impractical to obtain a sufficiently large sample of runs. For such situations, Stephenson et al (2002) describe an alternative technique, based on Bayesian statistics, for computing the output distribution using far fewer model runs.

Once the uncertainty in the model output has been quantified in PSA by its probability distribution, the natural way to express uncertainty about cost-effectiveness is again through the cost-effectiveness acceptability curve. As mentioned already, this is another intrinsically Bayesian construction.

A natural response to uncertainty about cost-effectiveness is to ask whether obtaining further data might reduce uncertainty. In the United Kingdom, for instance, one of the decisions that NICE might make when asked to decide on cost-effectiveness of a drug is to say that there is insufficient evidence at present, and defer approving the drug for reimbursement by the National Health Service until more data have been obtained. Bayesian decision theory provides a conceptually straightforward way to inform such a decision, through the computation of the expected value of sample information.

Expected value of information calculations have been advocated by Felli and Hazen (1998), Claxton and Posnett (1996), Brennan et al (2003) and a Bayesian calculation for complex models developed by Oakley (2002). There is a strong link between such analyses and design of trials, since balancing the expected value of sample information against sampling costs is a standard Bayesian technique for identifying an optimal sample size.

There is another important link between the analysis of economic models and the analysis of cost-effectiveness trials. Where the evidence for individual parameters in an economic model comes from a trial or other statistical data, the natural distribution to assign to those parameters is their posterior distribution from a fully Bayesian analysis of the raw data. This assumes that the data are directly relevant to the parameter required in the model, rather than relating strictly to a similar, but different, parameter. In the latter case, it is simple to link the posterior distribution from the data analysis to the parameters needed for the model, using structural prior information.

This linking of statistical analysis of trial data to economic model inputs is a form of **evidence synthesis** and illustrates the holistic nature of the Bayesian approach. Examples are given by Ades and Lu (2002) and Cooper et al (2002). Ades et al synthesize evidence from a range of overlapping data sources within a single Bayesian analysis. Synthesizing evidence is exactly what Bayes' theorem does.



Conclusions

In this section we will briefly summarize the main messages being conveyed in this Primer.

- Bayesian methods are different from and, we posit, have certain advantages over conventional frequentist methods, as set out in benefits (B1) to (B5) of the *Overview*. These benefits are explored and illustrated in various ways throughout subsequent sections of the Primer.
- There are some perceived disadvantages of Bayesian methods, as set out in the drawbacks (D1) to (D3) in the *Overview*. These are also discussed in subsequent sections and we describe how they are being addressed. It is up to the reader to judge the degree to which the benefits may outweigh the drawbacks in practice.
- Bayesian technologies have already been developed in many of the key methodologies of health economics. Already we see clear advantages in the design and analysis of cost-effectiveness trials, quantification of uncertainty in economic models, expression of uncertainty about cost-effectiveness, assessment of the value of potential new evidence, and synthesis of information going into and through an economic evaluation.
- There is enormous scope for the development of new and more sophisticated Bayesian techniques in health economics and outcomes research. We are confident that Bayesian analysis will increasingly become the approach of choice for the development and evaluation of submissions on cost-effectiveness of medical technologies, as well as for pure cost or utility studies.



Bibliography and Further Reading

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Further reading on Bayesian statistics

Preparatory books.

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Lee, P.M. (1997). *Bayesian Statistics: An Introduction*, 2nd ed., Arnold, London.

More advanced texts.

At an intermediate level, Migon and Gamerman is a nice, readable but concise book. Congdon concentrates on how to develop models and computations for the practical application of Bayesian methods. The last two books, by Bernardo & Smith, and by O'Hagan, are the most advanced, for people wishing to learn Bayesian statistics in depth.

Migon, H. S. and Gamerman, D. (1999). *Statistical Inference: An Integrated Approach*. Arnold, London.

Congdon, P. (2001). *Bayesian Statistical Modelling*. John Wiley.

Bernardo, J. M. and Smith, A. F. M. (1994). *Bayesian Theory*. Wiley, New York.

O'Hagan, A. (1994). *Bayesian Inference*, volume 2B of "Kendall's Advanced Theory of Statistics". Arnold, London.

Philosophy

Finally, the following presents the case for Bayesian inference from the perspective of philosophers of science.

Howson, C. and Urbach, P. (1993). *Scientific Reasoning*, 2nd edition. Open Court; Peru, Illinois.



Appendix

This Appendix offers more detailed discussion of the issues raised in the first four sections of this Primer.

Inference – Details

The following subsections give details of the arguments presented in the “*Inference*” section and of the key differences between Bayesian and frequentist statistics identified in Table 1.

The nature of parameters

The most fundamental distinction between the Bayesian and frequentist approaches is that in the Bayesian approach the unknown parameters in a statistical model are random variables. Accordingly, in a Bayesian analysis the parameters have probability distributions, whereas in frequentist analysis they are fixed but unknown quantities, and it is not permitted to make probability statements about them.

This can be puzzling to the layman because a standard frequentist statement like a confidence interval certainly seems to be making probability statements about the unknown parameter. If we see the statement that [3.5, 11.6] is a 95% confidence interval for a parameter μ , surely this is saying that there is a 95% chance that μ lies between 3.5 and 11.6. No, it cannot mean this because μ is not a random quantity in frequentist inference. We shall see what it does mean when we discuss *The nature of inferences*.

In Bayesian statistics, the parameters do have probability distributions, and if a Bayesian analysis produces a 95% interval then it **does** have exactly the interpretation that is usually put on a confidence interval.

The nature of probability

Underlying this distinction between the two approaches to statistics over the nature of parameters is a difference in how they interpret probability itself. In frequentist statistics, a probability can only be a long-run, limiting, relative frequency. This is the familiar definition used in elementary courses, often motivated by ideas like tossing coins a very large number of times and looking at the long-run, limiting frequency of 'heads'. It is because it is based firmly on this frequency definition of probability that we call those traditional methods 'frequentist'. Bayesian statistics, in contrast, rest on an interpretation of probability as a personal degree of belief. Although to some this may seem 'woolly' and unscientific, it is important to recognize that Bayesian statisticians have widely and successfully developed analyses based on this interpretation. As explained in *Prior Information*, it does not lead to unbridled subjectivity and unscientific practices.

The necessity of such an interpretation becomes clearer when we appreciate how many events that we would be willing to consider having probabilities could never have a frequentist probability. The probability of a hypothesis is an obvious example, since a particular hypothesis either is or is not true, and we cannot consider any experimental repetitions of it like we could for tossing a coin. Some other examples are the probability of rain tomorrow or the probability that you will experience a myocardial infarction (MI) during your lifetime. Tomorrow is a unique day, with meteorological conditions preceding it today that have not existed in precisely the same form before, and never will again, and you are a unique person whose genetic makeup and lifestyle make you more or less disposed to MI at some point in your life in a way not precisely matched by anyone else. Despite their uniqueness, we generally have no difficulty in thinking of these events as having probabilities. Most of the uncertain events and variables of real interest to scientists and practitioners are one-off things, and the frequency interpretation of probability is completely unable to accommodate our wish to describe them by probabilities.

The nature of inferences

Probabilities in the frequentist approach must be based on repetition. The statement that [3.5, 11.6] is a 95% confidence interval for a parameter μ says

that if we repeated this experiment a great many times, and if we calculated an interval each time using the rule we used this time to get the interval [3.5, 11.6], then 95% of those intervals would contain μ . The 95% probability is a property of the **rule** that was used to create the interval, not of the interval itself. It is simply not allowed, and would be wrong to attribute that probability to the actual interval [3.5, 11.6]. This is a very unintuitive argument. Frequentist statements such as these are widely misinterpreted, even by trained statisticians. The erroneous interpretation of the confidence interval, that there is a 95% chance of the parameter μ lying in the particular interval [3.5, 11.6], is almost universally made by statistician and non-statistician alike. Nevertheless, it is incorrect. A Bayesian interval, however, does have that interpretation.

The Bayesian approach uses different terminology from the familiar frequentist terms. Bayesian intervals are generally called *credible intervals* to make it clear that they are different from confidence intervals. The *highest density interval* is a credible interval with the property of being shortest among all available credible intervals with a given probability of containing the parameter's true value.

An entirely similar argument can be made about frequentist significance tests. If a hypothesis is rejected with a P-value of 1%, this does **not** mean that the hypothesis has only a 1% probability of being true. Hypotheses do not have probabilities in a frequentist analysis any more than parameters do. The P-value must again be based on repetition of a rule. In this case it is a rule which says that when the data satisfy some condition we will formally reject the hypothesis. The P-value's proper interpretation is that if we repeated the experiment many times, and if the hypothesis really were true every time, then on only 1% of such experiments would the rule lead us to (wrongly) reject that hypothesis. This is a tricky and convoluted idea. It is not surprising that practitioners regularly misinterpret a P-value as the probability that the hypothesis is true.

To interpret a P-value in this way is not only wrong but also dangerously wrong. The danger arises because this interpretation ignores how plausible the hypothesis might have been in the first place. Here are three examples.

Examples.

- 1) Screening. Consider a screening test for a rare disease. The test is very accurate, with false-positive and false-negative rates of 0.1% (i.e. only one person in a thousand who does not have the disease will give a positive result, and only one person in a thousand with the disease will give a negative result). You take the screen and your result is positive. What should you think? Since the screen only makes one mistake in a thousand, doesn't this mean you are 99.9% certain to have the disease? In hypothesis testing terms, the positive result would allow you to reject the null hypothesis that you don't have the disease at the 0.1% level of significance, a highly significant result agreeing with that 99.9% diagnosis. But the disease is rare, and in practice we know that most positives reporting for further tests will be false positives. If only one person in 50,000 has this disease, your probability of having it after a positive screening test is less than 1 in 50.

Although this example may not be obviously concerned with hypothesis testing, in fact there is a direct analogy. We can consider using the observation of a positive screening outcome as data with which to test the null hypothesis that you do not have the disease. If the null hypothesis is true, then the observation is extremely unlikely, and we could formally reject the null hypothesis with a P-value of 0.001. Yet, the actual probability of the null hypothesis is more than 0.98. This is a dramatic example of the probability of the hypothesis (> 0.98) being completely different from the P-value (0.001). The difference clearly arises because the null hypothesis of you having the disease begins with such a low prior probability. Nobody who is familiar with the nature of screening tests would be likely to make the mistake of interpreting the false positive rate as the probability of having the disease (but it is important to make the distinction clear to patients!) By the same token, it is wrong to interpret a P-value as the probability of the null hypothesis, because this fails to take account of the prior probability in exactly the same way.

- 2) Subgroup analysis. Statisticians are continually warned against trawling through the data for significant subgroup effects. In clinical trials, subgroup analyses are generally only permitted if they were prespecified and have a plausible biological mechanism. This is a clear case where it is recognized that the interpretation of significance depends on how plausible the hypothesis was in the first place.
- 3) Drug development. Pharmaceutical companies synthesize huge numbers of compounds looking for clinical effects. By analogy with the screening example, even after a trial has produced an effect that is highly significant, the probability that this effect is real may not be large; we expect false positives. Despite this, and despite the experience of many drugs going into expensive Phase III trials only to prove ineffective, companies continue to wrongly and over-optimistically interpret significant P-values.

In contrast to the frequentist approach, a Bayesian analysis can give a probability that a hypothesis is true or false. A Bayesian hypothesis test does just that – reports the probability that the hypothesis in question is true. A proper Bayesian analysis would correctly identify the probabilities in all the above examples.

Frequentist point estimates are also based on repetition, and although they are less often misinterpreted in Bayesian ways, there are still important differences. Suppose that a frequentist analysis reports that an unbiased estimate of μ is 9.1. Unbiasedness is a property of the *rule* of estimation, not of the estimate itself, and in this case means that if we repeated the experiment many times and applied the same rule each time to produce an estimate of μ , then the average value of these estimates would be μ itself. On average, the estimates will be neither too high nor too low, but nothing is or can be said about whether 9.1 is expected to be too high or too low. A Bayesian analysis might report that 9.1 is the expected value of μ and has precisely the interpretation that 9.1 is not expected to be too high or too low as an estimate of μ .

Example.

Consider the rate of side effects from a drug. In a trial with 50 patients, we observe no side effects. The standard unbiased estimator of the side effect rate per patient is now zero (0/50). In what sense can we believe that this is “on average neither too high nor too low”? It obviously cannot be too high and is almost certain to be too low. It is true that the estimation **rule** (which is to take the number of patients with side effects and divide by 50) will produce estimates that on average are neither too high nor too low if we keep repeating the rule with new sets of data. It is also clear, though, that we cannot apply this interpretation to the individual estimate. To do so is like interpreting a P-value as the probability that the null hypothesis is true; it is simply incorrect. In any Bayesian analysis, given no side effects among 50 patients, the expected side effect rate would be positive. Furthermore, the posterior expectation has the desired interpretation that **this estimate** is expected to be neither too high nor too low.

More natural and useful inferences

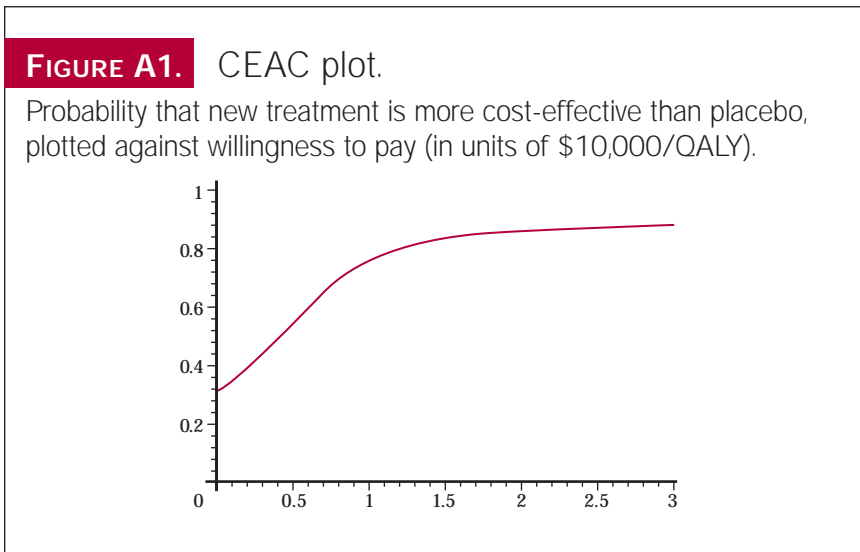
In frequentist inferences the words ‘confidence’, ‘significance’ and ‘unbiasedness’ are **technical** terms, and it is important to interpret them according to their definitions.

The fact that practitioners invariably, but incorrectly, wish to interpret a confidence interval as making a probability statement about the parameter is evidence that the Bayesian approach is more intuitive and natural and gives more direct answers to the client’s questions. It is similarly tempting to interpret a P-value as the probability that a hypothesis is true, because this is exactly what the practitioner wants to hear. Again, the Bayesian inference naturally and directly addresses the practitioner’s needs.

This is the key benefit (B1) – “more natural and useful inferences” – of the *Overview* section. It is easy to see how it becomes a very real benefit for the health economist. For instance, one widely used way of presenting a cost-effectiveness analysis is through the Cost-Effectiveness Acceptability Curve (CEAC),

introduced by van Hout et al (1994). An example is shown in Figure A1. For each value of the threshold willingness to pay λ , the CEAC plots the probability that one treatment is more cost-effective than another.

It should already be clear to the reader that this probability can only be meaningful in a Bayesian framework. It refers to the probability of a one-off event (the relative cost-effectiveness of these two particular treatments is one-off, and not repeatable), and that event is expressed in terms of the unknown parameters of the statistical model used to analyze the available evidence. We note that it is possible to construct a frequentist alternative CEAC, defined in terms of P-values (O'Hagan et al, 2000; Löthgren and Zethraeus, 2000), and which plots for each value of λ , the probability that the data would have fallen into a set bounded by the observed data, assuming the truth of the hypothesis that the two treatments are equally cost-effective. However, it would seem rather perverse to adopt that frequentist approach when a Bayesian analysis yields the far more direct and useful CEAC that plots the probability that treatment 2 is more cost-effective than treatment 1.



The Bayesian Method – Details

The following subsections give more details of the Bayesian method.

Bayes' theorem

The simplest way to express Bayes' theorem without using mathematical notation is this:

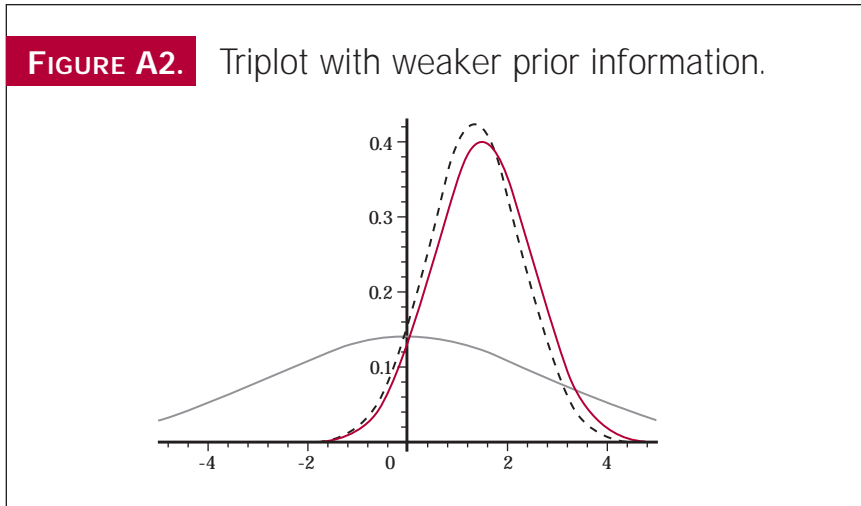
The posterior is proportional to the prior times the likelihood.

Several terms in this statement need to be defined and explained. It will be useful to refer to Figure 1 in the box 'Example of Bayes' theorem'. 'The posterior' means the posterior distribution of the unknown parameter(s). Strictly, it is the posterior probability density function, which is shown as the black dotted curve in Figure 1. Similarly, 'the prior' means the prior distribution of the unknown parameter(s), also in the form of the prior probability density function and shown as the grey line in Figure 1. The 'likelihood' is the common factor in both frequentist and Bayesian theory. It represents the information in the data and is shown as the red curve in Figure 1. Formally, for any given value of the unknown parameter, the likelihood plots the probability of observing the data that were actually observed. Bayes' theorem states that we should multiply the two curves. Since the area under any probability density curve must be equal to one we scale the product to satisfy this condition, which Bayes' Theorem expresses by saying that the posterior is 'proportional to' the product. Thus, the black dotted curve in Figure 1 results from multiplying the grey and red curves and scaling the result so that the area under it is equal to one.

This mechanism of multiplying the two curves also makes it clear that Bayes' theorem weights each source of information according to its strength. Consider the situation in which the prior information is very weak. This would be represented by a very flat grey curve, giving more or less equal prior probability to a wide range of parameter values. When we apply Bayes' theorem, then the posterior becomes almost a constant times the likelihood, and because

it must be scaled to integrate to one, the posterior is in effect the same as the red curve. This is shown in Figure A2, where we have weakened the prior information relative to Figure 1.

When the prior information is very weak, relative to the data information, the prior distribution gets so little weight in Bayes' theorem that the posterior distribution is effectively just the likelihood. In this situation we might expect, and in simple problems often find, that Bayesian methods lead to similar inferences to conventional frequentist methods. Bayesian methods make use of more information than frequentist methods, but give each source of information its due weight; weak information is naturally downweighted.



Another useful feature of the Bayesian paradigm that is worth mentioning and nicely captured in a simple phrase is:

Today's posterior is tomorrow's prior.

The paradigm is about learning, and we can always learn more. When we acquire more data, Bayes' theorem tells us how to update our knowledge to synthesize the new data. The old posterior contains all that we know before see-

ing the new data, and so becomes the new prior distribution. Bayes' theorem synthesizes this with the new data to give the new posterior. And on it goes... Bayesian methods are ideal for sequential trials!

Bayes' theorem also makes it more clear as to why the common misinterpretation of frequentist inferences is wrong. The likelihood expresses the probability of obtaining the actual data, given any particular value of the parameter. In simple terms,

$$\text{Likelihood} = P(\text{data} \mid \text{parameters}).$$

This distribution is the basis of frequentist inference. On the other hand, the basis of Bayesian inference is the posterior distribution, which is the probability distribution of the parameters, given the actual data,

$$\text{Posterior} = P(\text{parameters} \mid \text{data}).$$

It is the unjustified switching around of parameters and data that leads to misinterpretations. For instance, a P-value is $P(\text{data} \mid \text{hypothesis})$, whereas what a decision-maker wants, and what Bayesian inference provides, is $P(\text{hypothesis} \mid \text{data})$. It is clear that the two are quite different things, and Bayes' theorem shows the relationship between them: we can only derive the posterior probability we want by combining the P-value with the prior distribution.

Bayesian inference

In the Bayesian approach, all inferences are derived from the posterior distribution. When a Bayesian analysis reports a probability interval (a credible interval) for a parameter, this is a **posterior** interval, derived from the parameter's posterior distribution, based not only on the data but also on whatever other information or knowledge the investigator possesses. The probability that a hypothesis is true is a **posterior** probability and a typical example of an estimate of a parameter would be the **posterior** mean (the 'expected' value).

These are the Bayesian analogues of the three kinds of inferences that are available in the frequentist framework. However, Bayesian inference is much more flexible than this.

Often the real question of interest does not fit one of these frequentist inference modes. For instance, the investigator frequently wants to know “What do we now know about this parameter, after seeing the data?” There is no straightforward frequentist answer to that very natural question. The Bayesian answer is simplicity itself – we plot the posterior density. Thus, the black dotted curve in Figure 1 fully expresses what is known about that parameter after synthesizing all of the available evidence.

Decision theory provides another good example of the flexibility of Bayesian inference. In this theory we have a set of possible decisions and a utility function that specifies how good it would be to make a particular decision if the parameters turned out to have particular values. For instance, for a hypothesis test we could define a utility function that said it would be good (high utility) to accept the hypothesis if it turned out to be true, or to reject it if it turned out to be false, but otherwise the utility would be low.

If we knew the parameters it would be easy to arrive at a decision – we would just choose the decision with the largest utility for those values of the parameters. However, the parameters are generally unknown. Decision theory says we should choose the decision with the highest (posterior) **expected** utility. This expectation is the average value of the utility, averaged with respect to the posterior distribution of the parameters. This is a technical statement, but the point is that there is no frequentist way to find that optimal decision. It is essentially a Bayesian construct and is yet another way that the posterior distribution allows us to answer the real question of interest.

For a health care provider (HCP) choosing between two alternative drugs, the **net benefit** is an appropriate utility function. The net benefit (strictly, the net monetary benefit) of a given drug is obtained by taking the drug’s mean efficacy, multiplying it by the price that the HCP is willing to pay for a unit increase in efficacy, and then subtracting the mean cost to the HCP of using this drug. The rule of maximizing expected utility then implies that the HCP should choose the drug with the larger **expected** net benefit. Equivalently, it should choose drug 2 if the expected incremental net benefit over drug 1 is positive (Claxton, 1999).

Prior Information – Details

The following subsections give more details of the discussion presented in the *Prior Information* section of the main text.

Subjectivity

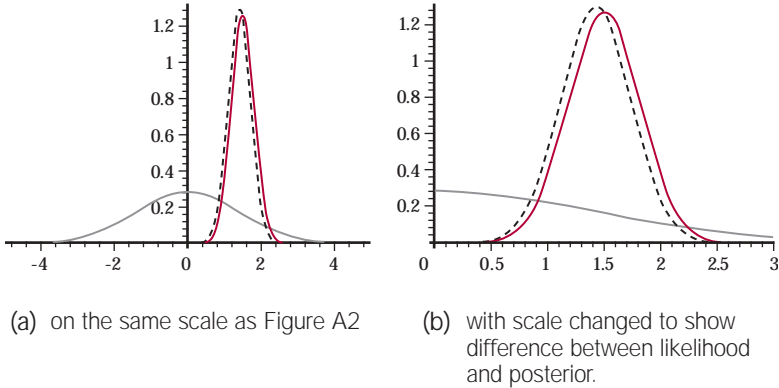
The fact that Bayesian methods are based on a subjective interpretation of probability was introduced in the subsection *The Nature of Probability* in this Appendix. We explained there that this formulation is necessary if we are to give probabilities to parameters and hypotheses since the frequentist interpretation of probability is too narrow. Yet this leaves Bayesian methods open to the charge of subjectivity, which is thought by many to be unacceptable and unscientific.

Yet science cannot be truly objective. Schools of thought and contention abound in most disciplines. Science attempts to minimize subjectivity through the use of objective data and reason, but where the data are not conclusive we have to use our judgement and expertise.

Bayesian methods naturally accommodate this approach. Figure 1 demonstrates how Bayes' theorem naturally weights each information source according to its strength. In that example, the data were only slightly more informative than the prior, and so the posterior is quite strongly influenced by the prior as well as by the likelihood.

We also saw in Figure A2 how if the prior information is weakened then Bayes' theorem effectively places all of the weight on the likelihood. Often we are in the more fortunate position of having strong data. Then the situation will be more like the triplot in Figure A3. As new data accumulate the prior distribution again becomes less influential.

FIGURE A3. Triplot with more informative data



In this case, the data are based on 10 times as much information as in Figure 1. The red likelihood curve is much narrower than the grey prior density. The prior contributes very little information to the synthesis, and the posterior density (black dotted curve) is almost identical to the likelihood. When the data are sufficiently strong they will outweigh any subjective prior information. Although different experts in the field might bring different prior knowledge and opinions, the data will outweigh their priors, and they will all agree closely on the posterior distribution. This is an excellent model for science.

What if the data are not conclusive in this way? Then different experts in the field will have materially different posterior distributions. We do not have consensus, although their differences will generally have been lessened by the data. It is actually a strength of the Bayesian approach that by considering the consequences of using different prior distributions we can see whether the data are adequate to outweigh those differences. If the data are not strong enough, then it would be misleading to present any analysis as if it were definitive.

Whose prior?

Suppose that a sponsor of some medical technology (e.g. a pharmaceutical company or device maker) wishes to present a Bayesian analysis in support of a case for cost-effectiveness of that technology. What would be acceptable in the form of prior information? One way to approach this question is to ask whose prior should be used.

As shown above, it may not matter. Consensus can be reached if the data are strong enough to overrule the differences in the prior opinions and knowledge of **all** interested parties. However, the argument does not work if one person has sufficiently strong prior information or opinions. It only takes one extremely opinionated person to prevent agreement. We are familiar with the person whose views on some matters are so prejudiced that they will not listen to any facts or arguments to the contrary – Bayes' theorem explains these people, too!

This clarifies some aspects of subjectivity. While we should accept that different people might legitimately have different background knowledge or might legitimately interpret the same information differently, there is no place for prejudice or perverse misinterpretation of the available facts in health economics (or anywhere else). An important aspect of Bayesian analysis is that the prior distribution is set out openly. If it is not based on reasonable use of information and experience, the resulting analysis will not convince anyone. This is the key benefit (B5) – “more open judgements” – of Bayesian analysis. All cards should be on the table and nothing hidden.

Returning to the question of whose prior a sponsor might use, it is likely that the sponsor's own prior distribution would be unacceptable. In principle, their opinions might be defensible on the basis of the company's own substantial experiences in development and testing of the product, but there is the risk of selective use of information unless full disclosure can be enforced. To quote the box “The Evidence” in the main text, the sponsor would need to be able to show that its prior not only represented the evidence but also the whole evidence.

The most natural choice of prior distribution might be the considered and defensible prior of an expert in the field. The agency to which the cost-effec-

tiveness case is being made would probably be interested in whether the inferences might change if the views of alternative experts were considered. Ideally, some kind of consensus view of the profession would be a good choice.

Examples

These ideas are illustrated in the following two examples, which are discussed briefly in the main text.

Subset analysis is a notoriously tricky question. The risk of dredging the

	NAMES A-D	NAMES E-Z
<i>Treatment 1</i>	\$800	\$800
<i>Treatment 2</i>	\$450	\$850

data to find subgroups of patients that respond differently is real. For example, suppose that a cost study found the following mean costs table (Table 2), split by treatment and the initial letter of the patient's surname.

It looks like treatment 2 is cheaper for patients whose names begin with the letters A to D. There is highly unlikely to be any plausible reason for such a subgroup effect. To avoid the risk of declaring spurious subgroup effects, standard clinical trials guidance requires that the analysis of possible subgroups must be specified before a trial begins, and there must be a plausible mechanism for the proposed subgroup effects.

From a Bayesian perspective, the absence of a plausible mechanism simply constitutes prior information – the subgroup effect would have a very small prior probability. Combining the prior information with the data would result in a small posterior probability, regardless of how convincing the data appeared to be. The prior information is strong enough to override the data. The standard guidance, therefore, applies equally to Bayesian analyses; subgroup analyses must be prespecified, so that prior information about their plausibility can be quantified.

Bayesian methods will then automatically moderate the data and prevent us from claiming implausible effects that arise by chance in the data. The prior information is clearly important. To an extent, the existing procedures for frequentist subgroup analysis incorporate the prior information (and so, we would argue, are unconsciously Bayesian). However, the frequentist analysis simply splits subgroup hypotheses into those that are plausible a priori and those that are not, whereas the Bayesian assigns a prior probability that can take any value from 0 to 1, and thereby allows a far more subtle gradation.

Hospitalization. Suppose that, after evaluating good evidence on efficacy of a new drug relative to the standard treatment, a decision on whether it is more cost-effective rests on whether it reduces hospitalizations. Here the data come from a trial in which the number of days in hospital was recorded for each of 100 patients in each treatment group. A total of 25 hospital days were recorded in the standard treatment group and only 5 in the group receiving the new drug. In frequentist terms, the difference is found to be significant at the 5% level (one-sided). (We will not give technical details of calculations, but all of this, and subsequent analysis, may be reconstructed using the additional information that the sample variances were 1.2 in the standard treatment group and 0.248 in the new drug group.) The drug company could then, in conventional frequentist terms, claim an effect on hospitalization, estimate the mean number of days per patient as 0.25 under standard treatment and 0.05 under the new drug, perhaps with the result that the new drug is now found to be more cost-effective than standard treatment.

This is, however, a rather small trial and the data are far from conclusive. If other evidence were available it would be prudent to incorporate it in the analysis. Suppose that a much larger trial (in comparable conditions) of a similar drug produced a mean number of days in hospital per patient of 0.21, and that the standard error of this estimate is only about 0.03. This extra information suggests that the observed rate of 0.05 for the new drug is optimistic and casts doubt on the magnitude of the real difference between it and standard treatment. However, the interpretation of this evidence is necessarily judgmental. Nobody would claim that the two drugs should necessarily yield the same

hospitalization rates, but it is reasonable to suppose that they would not be markedly different. Because they cannot be treated as completely comparable with the trial data on the new drug, we cannot treat this other, larger trial as part of the data and just merge it with the new data. There is no apparent way to use the evidence on the related drug in a frequentist analysis. Yet any clinician or health care provider who was aware of this external evidence would be disinclined to take the new trial evidence at face value.

A Bayesian analysis resolves the question by treating the earlier trial as providing prior information but entails an element of subjectivity. Suppose that your interpretation of the prior information is that your prior expectation of the mean days in hospital for the new drug should be 0.21 but with a standard deviation of 0.08 to reflect the fact that the two drugs are not the same. Bayes' theorem now yields for you a posterior estimate of 0.095 for the mean hospital days using the new drug. There is still a reasonably strong probability (90%) that the new drug reduces this hospitalization rate, but now the estimated difference may not be large enough to provide the same assurance that it is more cost-effective than standard treatment.

The subjectivity in this analysis arises in the necessary judgement about how different the hospitalization rates might be for the two drugs. Another clinician or decision-maker might interpret the prior information differently and employ a different prior distribution. In particular, they may have a different prior standard deviation. In fact this answer is fairly robust to reasonable changes in the prior distribution. On that basis we might conclude that an 'objective' interpretation of the combined data is that there is a strong probability (perhaps around 90% but not as high as 95%) that the new drug reduces mean days in hospital but that it achieves a mean number of days nearer to 0.1 than to 0.05.

This example has shown how a Bayesian analysis, making use of genuine prior information and considering a range of reasonable interpretations of that information, can produce a scientifically sound conclusion. The answer differs substantially from the frequentist analysis which has no technical way of making use of the extra information. The Bayesian answer is also sound because it formalizes the natural intuitive reaction that anyone would have to the fre-

quentist analysis, knowing the result of the other trial.

In this and previous examples, we have stressed the power of the Bayesian approach to temper overly optimistic interpretations of P-values, but it is important to recognize that the reverse situation is equally common and important. Pharmaceutical company executives and biostatisticians will be very familiar with occasions where a Phase III trial of a drug has just failed to produce a significant effect, yet there is plenty of evidence (from related drugs, from a Phase II trial that was restricted to acute cases, etc.) to suggest that the drug really is effective. A properly conducted Bayesian analysis would allow the responsible incorporation of this additional evidence to demonstrate the drug's true efficacy. Both situations are of enormous importance to the developers and users of health care technologies –the first in avoiding costly mistakes due to being overly optimistic and the second in allowing beneficial products to be brought to market that otherwise would have to be abandoned or delayed for more testing.

Prior Specification – Details

The following subsections give details of three aspects of prior specification; the elicitation of expert priors, conjugate priors and the construction of structural priors.

Elicitation

We will consider the process of eliciting a prior distribution for an expert without reference to the actual nature of the underlying prior information. In practice, of course, the expert will base her analysis on that information, but in this subsection we will not try to deal with the specifics of the underlying information.

Suppose that we decide to formulate a prior distribution for a particular parameter (such as the mean utility gain arising from some treatment), representing the knowledge of a single expert about that parameter. The first difficulty we will face is that the expert will almost certainly not be an expert in probability or statistics. That means it will not be easy for this person to express her beliefs in the kind of probabilistic form demanded by Bayes' theorem.

Our expert might be willing to give us an estimate of the parameter, but

how do we interpret this? Should we treat it as the mean (or expectation) of the prior distribution, or as the median of that distribution, as its mode, or something else? In statistics, the mean, median and mode might all be regarded as sound point estimates of a quantity, but they are different things. The mean is the 'expected value', the median is the 'central value' and the mode is the 'most likely value'. In principle, we might explore with the expert these nuances of meaning, but for someone not trained in statistics it will not be easy for her to appreciate the differences and give us a reliable interpretation for her estimate.

We could go on to elicit from the expert some more features of her distribution, such as some measure of spread to indicate her general level of uncertainty about the true value of the parameter. (Remember, the strength of information is indicated by the narrowness of the distribution representing that information.)

The next difficulty is that no matter how much information of this type we extract from the expert it will not be enough to identify her distribution exactly. This is easy to see when we recognize that to uniquely identify the grey curve in Figure 1 representing the prior distribution, we must specify its height at every single point – potentially an infinite number of facts must be obtained from the expert. To compound this problem, the more detail we ask for, the more difficult it is for the expert. In practice, the best we can do is to elicit a few simple expressions of her knowledge, in the form of things like median and quartiles and then fit some sensible distribution to those statements.

Even the judgements that we elicit from the expert cannot be treated as precise. Suppose that the expert gives us the estimate of 0.85 for the parameter, and we interpret this as the mean of her prior distribution. Even if we are right to interpret it in that way, we cannot realistically treat it as a precise number. Our expert almost certainly gave us a round figure and couldn't say whether 0.86 might be a more accurate reflection of her prior mean. The reader should now amply appreciate the criticism (D2), that "prior specification is unreliable".

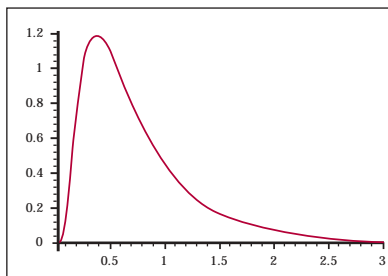
Nevertheless, there is a growing body of research into how to elicit experts' knowledge accurately and reliably. The difficulties that people face in assessing probabilities have been extensively studied, particularly by cognitive psycholo-

gists; some useful reviews can be found in Lichtenstein et al (1980), Meyer and Booker (1981), Cooke (1991), Kadane and Wolfson (1998). Although the psychologists have tended to emphasize the tasks that people conceptualize poorly, the practical significance of this work is that we know a great deal about how to avoid the problems. This and ongoing research seeks to identify the kinds of questions that are most likely to yield good answers, avoiding pitfalls that have already been identified by psychologists and statisticians, and the kind of feedback mechanisms that help to ensure good communication between statistician and expert.

The second answer is that, fortunately, the imprecision of distributions elicited from experts may not matter much. As discussed earlier, we can think of a range of prior distributions that are consistent with the statements we have elicited from the expert, and if the data are sufficiently strong then all these different specifications of the prior distribution will lead to essentially the same posterior distribution. The box “Example of elicitation” explores these ideas.

Example of Elicitation

An expert estimates a relative risk (RR) parameter to be about 50%, but has considerable uncertainty about its true value. She says that it is unlikely to be less than 0.2 or greater than 1.5. The distribution to the right fits those statements, but so would many other distributions. The question is whether, if we tried those other distributions in a Bayesian analysis of some data, they would give materially different posterior inferences.



Conjugate priors

As explained in the preceding discussion, the usual approach to specifying a prior distribution for some parameter consists of first specifying (or eliciting) a few features of the distribution, such as a prior expectation and some meas-

ure of prior uncertainty (e.g. the prior variance), then choosing a suitable distribution to fit these features. In the box “Example of elicitation”, for instance, a particular form of distribution known as a gamma distribution has been fitted to the expert’s two specific statements.

This may seem rather cavalier and arbitrary, but in practice the prior distribution is often quite well determined even if only a few actual features have been specified or elicited from the expert. Although the actual distribution chosen is arbitrary, any other reasonable prior distribution that fits the specifications is likely to be very similar, and hence to lead to very similar inferences or decisions.

It is then sensible to make the choice of distributions on grounds of simplicity and convenience. Mathematically, in some simple statistical problems there exist classes of priors known as *conjugate priors* that are particularly convenient. This is because of two features. First, if the prior distribution is a member of the relevant conjugate class then the posterior distribution will also be a member of that class. Second, the conjugate distributions are sufficiently simple for us to be able to derive a great many inferences from them without resort to computational methods. Whenever the statistical model is such that a conjugate family exists and a member of that family fits the prior specification, then it is particularly convenient to choose that distribution. Very simple posterior analysis then follows.

Indeed, in the early days of modern Bayesian statistics, in the 1960s and 1970s, Bayesian analysis was essentially restricted to the use of conjugate priors, since computational tools did not exist to tackle more complex situations. They are now much less used because statisticians are building models that do not have corresponding conjugate priors, and the desire for more realistic formulation of prior information also means that conjugate priors may not fit even when they are available.

Structural priors

Structural prior distributions express information about relationships between parameters, usually without saying anything about the specific values of individual parameters. For instance, we might specify a prior distribution that

represents effective ignorance about the mean cost under two different treatments, but says that we expect the ratio of these means to be in the range 0.2 to 5. The mean cost under any given treatment could be anything at all, but whatever value it actually takes we expect the mean cost under the other treatment will be within a factor of 5 of this.

A simple example is the prior distribution in the example of hospitalization. This can be dissected into two parts. We have substantial prior information about mean days in hospital under the related drug, and we have structural prior information about how it might differ from the corresponding mean hospitalization under the new drug. Indeed, if the raw data of the earlier trial are available we might formally analyze these as data with the results of the new trial. In that case, the prior information is purely structural. The framework now looks a little like a meta-analysis, and indeed Bayesian meta-analysis is based strongly on structural prior information.

In a Bayesian meta-analysis, we have several datasets, each of which addresses the efficacy of a treatment in slightly different conditions. So we have a separate parameter for mean efficacy in each trial, but we formulate a structural prior representing the prior expectation that these parameters should not be too different. This is usually done in a **hierarchical** model, where a common ‘underlying’ mean efficacy parameter is postulated, and each of the trial mean efficacies is considered to be independently distributed around this common parameter.

The hierarchical structure, introducing one or more common parameters, is often used to link several related parameters and to express a belief that they should be similar via the fact that they should all be similar to the common parameter. Another example is to formulate structural prior information that cost data arising in different arms of a trial should not be markedly different in their degrees of skewness. This has the benefit of moderating the influence of a very small number of patients with unusually high costs.

Computation – Details

The following subsections give details of Bayesian computation and its ability to address very complex models.

Complexity

The source of the extra complexity in Bayesian analysis is again the prior distribution. Suppose that the problem is the simple, canonical, statistical problem of estimating the mean of a normal distribution (with known variance), given a sample from that distribution. To the frequentist, this is a complete specification of the problem, and in principle there can be a single answer (and in fact the sample mean is universally accepted as the best estimate). To the Bayesian, the specification is incomplete because we also need to state the prior distribution. Then the answer will synthesize the two information sources and will depend on the prior. Given this simple problem, the Bayesian approach can give a very wide range of answers.

This makes the construction of Bayesian software very difficult. The software itself must be more complex. The reason for this is because it must allow for specification of the prior (which could be any distribution at all) and must be able to compute the desired inferences no matter what that prior distribution may be.

Mathematically, Bayesian inferences usually require us to be able to integrate the product of the prior and the likelihood. We have to do this, for instance, just to find the area under the curve, so as to know how to scale it to make that area 1. Just applying Bayes' theorem demands integration. More integration is then needed, for instance, to find the posterior mean or the probability that a hypothesis is true. Now even if the prior and the likelihood are individually quite nice functions whose integrals are well known, the product will almost invariably be sufficiently complex for us to be unable to derive the necessary integrals by mathematical principles. So these integrals need to be done numerically (for an introduction to the ideas and methods of numerical integration, see Thisted, 1988). The main reason why Bayesian methods were impractical until the 1990s was that we did not have effective integration algorithms. The reason for the subsequent explosion of Bayesian applications is that a very powerful, general solution was developed.

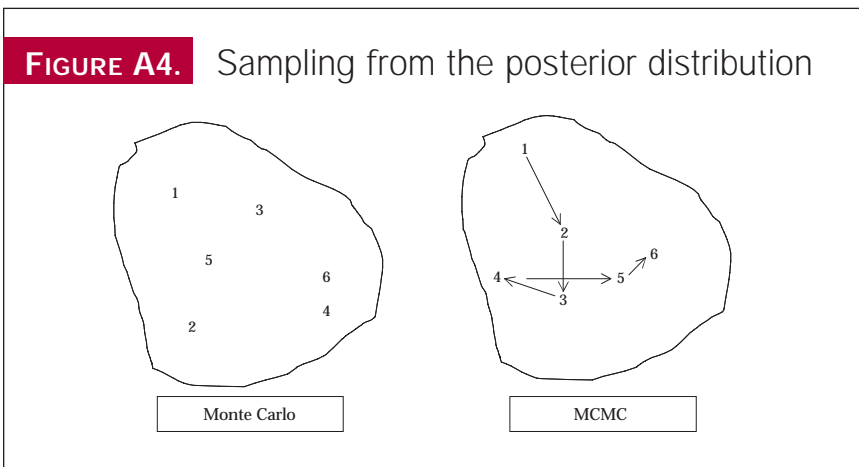
MCMC

The technique that has revolutionized Bayesian computation is *Markov chain Monte Carlo* (MCMC). The idea of MCMC has been outlined in the main

text: Bayesian inference is solved by randomly drawing a very large sample from the posterior distribution. Any inference we want to obtain from the posterior distribution we can calculate from the sample.

At this stage, it may be helpful to emphasize that we are not talking about the sample data. (Usually, we have little control over how many data we can get, and we don't expect to have such an enormous sample that we can calculate anything we like from the sample in this simple way.) Instead, we are talking about artificially generating a sample of *parameter* values, by some random simulation method that is somehow constructed to deliver a sample from the posterior distribution of those parameters.

Strictly speaking, the idea of drawing a large sample from the posterior distribution is called Monte Carlo. Monte Carlo simulation is used very widely in science as a powerful indirect way of calculating things that direct mathematical analysis cannot solve. What makes MCMC different is the way the sample is drawn. Simple Monte Carlo can be visualized as playing darts – ‘throwing’ points randomly into the space of all possible values of the parameters, with each point independent of the others. This approach is impractical for Bayesian analysis because in a model with many parameters it is extremely difficult to construct an efficient algorithm for randomly ‘throwing’ the points according to the desired posterior distribution. MCMC operates by having a point wandering around the space of possible parameter values. See Figure A4.



Technically, a probability model called a Markov chain generates this wandering point. Successive steps in this Markov chain produce the sample. It turns out that it is really quite simple to construct a Markov chain such that the sample is drawn from any desired posterior distribution.

The power of Bayesian computations derives from the availability of MCMC solutions to compute posterior inferences from almost arbitrarily complex statistical models with almost arbitrarily huge numbers of parameters. However, this simple statement hides some important complications.

It is clear that these successive values are connected and not independent in the way that simple Monte Carlo points are. If there is too much dependence, then the points move very slowly around the space of possible parameter values. Therefore, an extremely large sample will be needed to cover the space properly to represent the posterior distribution adequately. So the efficiency of MCMC methods depend critically on getting a Markov chain that moves rapidly around the space (a property that is referred to as 'good mixing'). Unfortunately, although it is generally very easy to devise an MCMC algorithm that works in principle, it often requires considerable skill and experience to construct one that mixes well.

Another complication is that the algorithms require a 'burn-in' period, for the randomly moving point to settle into the part of the parameter space supported by the posterior distribution. It is by no means simple to diagnose when the Markov chain has run long enough.

In a very wide range of moderately complex models (such as those that can be implemented successfully in the software *WinBUGS* described in the main text), these problems are minimal. For large and complex problems, however, MCMC remains something of an arcane art. Nevertheless, there is growing familiarity with the technique based on its widespread use in Bayesian statistics – and a growing literature on MCMC algorithms that is gradually advancing the frontier of problems that can be tackled routinely.

Tackling hard problems

There is a frequentist parallel to the computational problems of Bayesian methods, which is that it is extremely difficult to obtain exact frequentist tests, confidence intervals and unbiased estimators except in really simple models. It is often overlooked that the great majority of frequentist techniques in general use are, in fact, only approximate. This includes all methods based on generalized linear models, generalized likelihood ratio tests, bootstrapping and many more. The honorable exception is inference in the standard normal linear model. Even here, it is not straightforward to compare non-nested models using frequentist methods.

As described in the main text, the availability of computational techniques like MCMC makes exact Bayesian inferences possible even in very complex models. As statisticians strive to address larger, more complex data structures (micro-array data, data mining, etc), the benefit (B3) – “ability to tackle more complex problems” – of Bayesian methods becomes increasingly important.

