Medical Diagnosis Using Influence Diagrams

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Influence diagrams are used to illustrate how the probability of having a disease can be updated given the results from two or more clinical tests. The problem of calibrating a register using results from a survey, as discussed by Heldal and Spjøtvoll (1988), is solved using a Bayesian approach.

1. INTRODUCTION

The present article is a natural sequel to Pereira [4]. In that article, the problem of predicting (diagnosis) whether a certain disease is present, D, or absent, D', based on the result of a medical test was discussed. Here, we consider a problem where two clinical tests are available. D is for a severe form of the disease, and D' is for a less severe form.

The data in Table 1 and analyzed in this paper are from the Hospital das Clínicas, São Paulo. The data refer to 100 children with biliary obstruction. Biliary obstruction can take two forms: intra-hepatic, D, (there were 50 sample units) and extra-hepatic, D', (also with 50 sample units). If the diagnosis is intra-hepatic, then an operation on the liver is required, otherwise not. To help discriminate between the states D and D', two clinical tests are available. Both tests can give either positive or negative results. When the two tests are taken by a patient, the evidence can be one of the four possible indicants, represented by $(+,+)$, $(+,-)$, $(-,+)$, and $(-,-)$. However, for some of the patients, only the response to the first test is obtained, producing either evidence $(+,.)$ or $(-,.)$. For five of the children with state D in our sample, only the response to the first test was obtained and all had a positive response $(+,.)$. On the other hand, for two children with state D', only negative responses for the first test $(-,.)$ were obtained.

One problem is to determine the sensitivity and specificity of the tests; i.e., to evaluate the probability that a test will be positive (negative) when the test subject has (does not have) the disease. We are also interested in the problem

NETWORKS, Vol. 20 (1990) 565–577

CCC 0028-3045/90/050565-013$04.00

TABLE I. Frequencies of indicants in children with biliary obstruction.

	Intra-hepatic, D			Extra-hepatic, D'		
2nd \ 1st	(+,.)	(−,.)	Sum	(+,.)	(−,.)	Sum
(.,+)	28	01	29	02	02	04
(.,−)	12	04	16	09	35	44
Sum	40	05	45	11	37	48
Only 1st test	05	00	05	00	02	02
Total 1st test	$45 = x$	05	$m = 50$	11	$y = 39$	$n = 50$

of prediction, i.e., to evaluate the probability that a new patient, a child with biliary obstruction, who either responded to the first test only or to both tests, has D (or D'); that is, with the experience learned from the data in Table I, how can we evaluate the diagnostic probability represented by $Pr\{D|\text{evidence}\}$, where evidence is the result of a clinical test or tests on a new patient? The objective of this article is to answer this question.

In Section 2, we first discuss the general problem of prediction for a finite categorical population when incomplete data is presented. There we discuss a situation only slightly more general than the one in Basu and Pereira [2]. The probability results used here are in that paper. We use influence diagram techniques as in Barlow and Pereira [1]. For a very general and complete discussion of the use of influence diagrams in medical situations, see [6]. Algorithms for influence diagrams are discussed in [5].

Probability distributions used in this article are the beta, the Dirichlet, the Bernoulli, the binomial, the multinomial, the beta-binomial, and the Dirichlet-multinomial. The multinomial probability model follows from judgments of partial exchangeability and to this extent may be considered a consensus probability model. The Dirichlet is the natural conjugate prior for the multinomial. All other distributions are derived from these two probability models. All the results needed here can be found in [2]. The following notation is used:

(i) $p \sim Be(a,b)$ indicates that the quantity p has a distribution with parameters $a \geq 0$ and $b \geq 0$;

(ii) $\vec{p} \sim D_k(\vec{a})$ indicates that the k-vector has the Dirichlet distribution with nonnegative parameter vector $\vec{a}$;

(iii) $x|p \sim Ber(p)$ indicates that for fixed p the random quantity x has a Bernoulli distribution with parameter p;

(iv) $x|p \sim bi(m,p)$ indicates that for fixed p the random quantity x has a binomial distribution with parameters m and p;

(v) $\vec{x}|\vec{p} \sim M_k(m,\vec{p})$ indicates that for fixed $\vec{p}$ the k-vector (with integer coordinates) $\vec{x}$ has a multinomial distribution with parameters m and $\vec{p}$;

(vi) $x \sim Bb(m{:}a,b)$ indicates that x has a beta-binomial distribution with parameters m and (a,b); and

(vii) $\vec{x} \sim DM_k(m,\vec{a})$ indicates that the k-vector $\vec{x}$ has a Dirichlet-multinomial distribution with parameters m and $\vec{a}$.

2. COMBINATION OF SURVEYS AND REGISTERS: A BAYESIAN PERSPECTIVE

In this section, we present a Bayesian solution to the simple problem studied, from a frequentist perspective, by Hedal and Spjøtvoll [3]. The notation we use here permits one to visualize, without much effort, the extension to any larger two-way table. In Section 3, the results obtained here will be directly applied to our medical problem.

Let A_1 and A_2 be the two possible disjoint states (in general, we can have $L > 2$ states) for any particular unit of a population of finite size M. In the population, each unit is registered as being in one of two disjoint categories, B_1 or B_2 (here also we could also consider $K > 2$ categories). To fix ideas we could consider $A_1(A_2)$ as disease $D(D')$ and $B_1(B_2)$ as the positive (negative) response to a test. In this case, a positive response would correspond, in Hedal and Spjøtvoll's language, to registration (wrongly sometimes) of a unit as having D. In Section 3, however, we consider the A's as the results from the first test and the B's as the results from the second test. We return to this point later.

Suppose that a sample of size m is selected and each unit is classified properly as A_1 or A_2. From these, m sample units $m' \leq m$ are also classified properly as B_1 or B_2, whereas $m-m'$ are not classified with respect to the B categories; i.e., $m-m'$ observations are incomplete. Table II introduces the notation for the sample results.

To analyze the data in Table II we need to make additional judgments to determine an appropriate probability model. Suppose that in our judgment the m_{ij} sampled units are **exchangeable,** conditional on being in the category corresponding to the intersection of categories B_i and A_j. Then it can be shown that the multinomial model corresponding to the parameters in Table III is the appropriate model (see [2]). It will be convenient to define $P = p_{11} + p_{21}$, $p_1 = p_{11}/P$, and $p_2 = p_{22}/(1 - P)$.

To calculate the likelihood, we need to make additional judgments relative to the $m - m'$ incomplete observations in Table II. There are many possible ways in which such data could arise. However, we will make the required additional judgments relative to the data of Table I, the medical example. Table II could correspond to the data under the column heading "Intra-hepatic, D"

TABLE II. Sample frequencies, m specified.

	A_1	A_2	Total of B
B_1	m_{11}	m_{12}	$m_{1.}$
B_2	m_{12}	m_{22}	$m_{2.}$
Sum	$m'_{.1}$	$m'_{.2}$	m'
Total of A	$m_{.1}$	$m_{.2}$	m

$m_{.1} - m'_{.1}$ are in category A_1 but the B category is unknown.

TABLE III. Multinomial probabilities.

	A_1	A_2	Marginal of B
B_1	p_{11}	p_{12}	p_1
B_2	p_{21}	p_{22}	p_2.
Marginal of A	$P = p_{.1}$	$1 - P$	1

as well as the data under the column heading "Extra-hepatic, D'" in Table I. For the data in Table I, not all the children who took the first test also took the second test. The children who took only the first test were too weak to go to the second test. Hence, the fact that they took only the first test is not informative relative to the second test. Thus, m and m' are fixed and we consider only $m_{.1}$, $m'_{.1}$, m_{11}, and m_{22} as random a priori. The likelihood using the multinomial model and the data in Table II is

$$L(P,p_1,p_2) = Pr\{m_{.1},m'_{.1},m_{11},m_{22}|m,m',P,p_1,p_2\}$$
$$\propto P^{m_{.1}}(1-P)^{m_{.2}}p_1^{m_{11}}(1-p_1)^{m_{21}}(1-p_2)^{m_{12}}p_2^{m_{22}}.$$

Table IV gives the unknown frequencies in the remaining population. For simplicity, we consider as population units only the units that were **not** selected for the sample. The population is divided into two groups: the sample (which is observed) and the units not in the sample (the unobserved group).

We have the following probability statements as a consequence of our exchangeability supposition (note that there is a one to one correspondence between $(p_{11},p_{12},p_{21},p_{22})$ and (P,p_1,p_2) since the sum of the elements of the first vector is 1.):

(i) $M_{.1}|(P,p_1,p_2)$ is distributed as $M_{.1}|P \sim bi(M,P)$ and $m_{.1}|(P,p_1,p_2)$ is distributed as $m_{.1}|P \sim bi(m,P)$.

(ii) $M_{11}|((P,p_1,p_2),M_{.1})$ is distributed as $M_{11}|(p_1,M_{.1}) \sim bi(M_{.1},p_1)$ and $m_{11}|((P,p_1,p_2),m'_{.1})$ is distributed as $m_{11}|(p_1,m'_{.1}) \sim bi(m'_{.1},p_1)$. Analogously, the same statements hold if we substitute subscript 2(1) for 1(2).

(iii) $(M_{.1},M_{11},M_{22})$ and $(m_{.1},m'_{.1},m_{11},m_{22})$ are conditionally independent given (P,p_1,p_2). This assumption comes from our practical example of Section 1. It was decided before the second test that seven (five in the D-population and two in the D'-population) of the patients were not in sufficiently good health to support the stress of the second test.

TABLE IV. Unknown frequencies in the unsampled population of units (M specified).

	A_1	A_2	Total of B
B_1	M_{11}	M_{12}	M_1.
B_2	M_{21}	M_{22}	M_2.
Total of A	$M_{.1}$	$M_{.2}$	M

To complete our prior assumptions, we only have to assess a joint probability distribution for the vector $(p_{11},p_{12},p_{21},p_{22})$. To obtain an analytical solution for our problem, we choose a prior in the class of Dirichlet distributions that is a conjugate class of priors for the multinomial. Our objective is to streamline the solution. However, the technique used here is not restricted to this class of distributions.

To say that $(p_{11},p_{12},p_{21},p_{22})$ is distributed as a Dirichlet distribution of 4th order with parameter $(a_{11},a_{12},a_{21},a_{22})$ is equivalent to saying that $P = p_{11} + p_{21}$ is beta with parameter $(a_{11} + a_{21},a_{12} + a_{22}) = (a_{.1},a_{.2})$, p_1 is beta with parameter (a_{11},a_{21}),p_2 is beta with parameter (a_{22},a_{12}), and, finally, P, p_1, and p_2 are mutually independent. These are well-known results [2]. To illustrate all the model restrictions described here, we present the influence diagram of Figure 1.

Our main objective is to obtain the conditional distribution of the frequencies of that part of the population that was unobserved (not in the sample) given the sample frequencies (the frequencies of that part of the population that was observed); that is, we must obtain the distribution of $(M_{.1},M_{11},M_{22})|(m_{.1},m'_{.1},m_{11},m_{22})$. To obtain this distribution, we perform the usual integration, with respect to the parameters P, p_1, and p_2, of the probability function of $(M_{.1},M_{11},M_{22})|(P,p_1,p_2)$ multiplied by the posterior density of the parameters, i.e., the density of $(P,p_1,p_2)|(m_{.1},m'_{.1},m_{11},m_{22})$. Note that this is so because $(M_{.1},M_{11},M_{22})$ and $(m_{.1},m'_{.1},m_{11},m_{22})$ are conditionally independent given (P,p_1,p_2). As described by our influence diagrams, the desired distribution is a composition of beta-binomial distributions. The derivation of these distributions is a direct application of the results described in [2].

Figure 2 is the influence diagram after performing the Bayes operations (arc reversals) to obtain the posterior distribution of the parameters. Finally, Figure 3 presents the influence diagram that solves our problem since it shows the

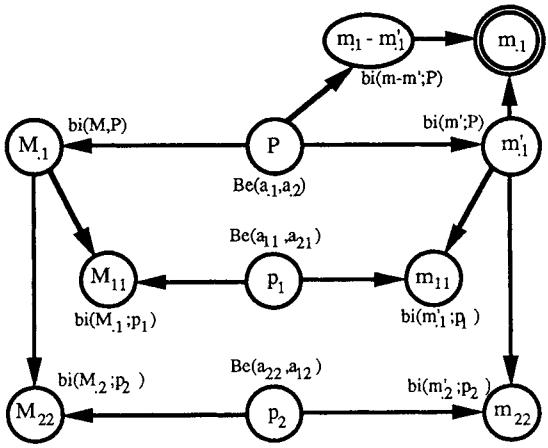

FIG. 1. Influence diagram modeling the finite population problem.

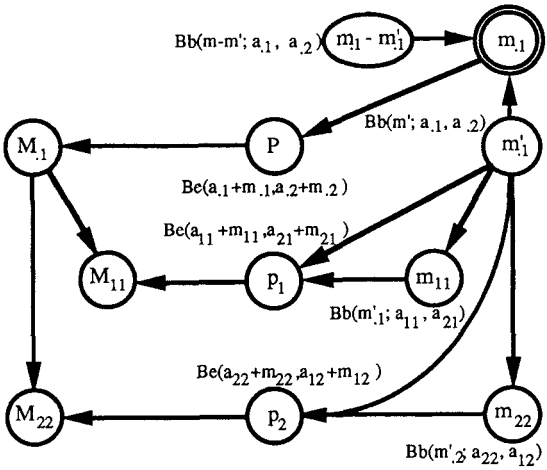

FIG. 2. Influence diagram generated after reversing some arcs in Figure 1. It includes only the modified distributions.

predictive distribution of the frequencies of the unseen population units, $M_{.1}$, M_{11}, and M_{22}, conditional on the sample observations, $m_{.1}$,$m'_{.1}$, m_{11}, and m_{22}.

The quantities of interest are the population frequencies that were not observed, namely, $M_{.1} = M - M_{.2}$, $M_{11} = M_{.1} - M_{21}$, and $M_{22} = M_{.2} - M_{12}$. These quantities, as shown in the influence diagrams, are distributed as beta-binomials. Their posterior expectations are

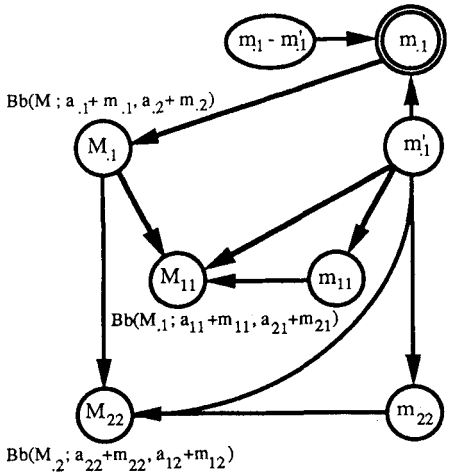

FIG. 3. Influence diagram generated after reversing some arcs in Figure 2 and eliminating nodes corresponding to unknown parameters.

$$(1)\quad \hat{M}_{.1} = E\{M_{.1}|m_{.1},m'_{.1},m_{11},m_{22}\} = E\{M_{.1}|m_{.1}\} = \frac{m_{.1} + a_{.1}}{m + a_{..}} M$$

$$\hat{M}_{.2} = M - \hat{M}_{.1},$$

$$(2)\quad E\{M_{11}|M_{.1},m_{.1},m'_{.1},m_{11},m_{22}\} = E\{M_{11}|M_{.1},m'_{.1},m_{11}\} = \frac{m_{11} + a_{11}}{m'_{.1} + a_{.1}} M_{.1},$$

$$(3)\quad E\{M_{21}|M_{.1},m_{.1},m'_{.1},m_{11},m_{22}\} = E\{M_{21}|M_{.1},m'_{.1},m_{21}\}$$

$$= M_{.1} - E\{M_{11}|M_{.1},m'_{.1},m_{11}\}$$

$$= \frac{m_{21} + a_{21}}{m'_{.1} + a_{.1}} M_{.1},$$

$$(4)\quad E\{M_{22}|M_{.1},m_{.1},m'_{.1},m_{11},m_{22}\} = E\{M_{22}|M_{.2},m'_{.2},m_{22}\} = \frac{m_{22} + a_{22}}{m'_{.2}+a_{.2}} M_{.2},$$

$$(5)\quad E\{M_{12}|M_{.1},m_{.1},m'_{.1}m_{11},m_{22}\} = E\{M_{12}|M_{.2},m'_{.2},m_{12}\}$$

$$= M_{.2} - E\{M_{22}|M_{.2},m'_{.2},m_{22}\}$$

$$= \frac{m_{12} + a_{12}}{m'_{.2} + a_{.2}} M_{.2}.$$

The expressions in (2)–(5) are the alternative Bayes estimators for the quantities of interest considered by Hedal and Spjøtvoll [3]. The interpretation of these simple results is very intuitive, contrary to the estimators of Hedal and Spjøtvoll. Note that we simply have to multiply the relative sample frequency, adjusted by the prior information, by the total of each of the subpopulation. These results can be easily extended. By replacing k for the first index and j for the second index, we have the results for a $K \times L$ table ($K > 2, L > 2$). Clearly, in this case, we would replace Dirichlet distributions for betas and multinomials for binomials.

From Figure 3 we can conclude that the conditional distributions of M_{11} and M_{22} given the data and $M_{.1}$ do not depend on the values for the missing data.

To obtain the Bayes' predictions for the cell frequencies without conditioning on the column marginals, $M_{.1}$ and $M_{.2}$, we only use the fact that $E\{X\} = E\{E\{X|Y\}\}$ and expressions (1) and (2). The final expressions for the cell frequencies are as follows:

$$\hat{M}_{11} = \frac{m_{11} + a_{11}}{m'_{.1} + a_{.1}} \hat{M}_{.1}, \qquad \hat{M}_{12} = \frac{m_{12} + a_{12}}{m'_{.2} + a_{.2}} \hat{M}_{.2},$$

$$\hat{M}_{21} = \frac{m_{21} + a_{21}}{m'_{.1} + a_{.1}} \hat{M}_{.1}, \quad \text{and} \quad \hat{M}_{22} = \frac{m_{22} + a_{12}}{m'_{.2} + a_{.2}} \hat{M}_{.2},$$

3. SOLUTION FOR THE MEDICAL PROBLEM

In this section we apply the results of Section 2 to the medical data presented in Table I. Note that we have two samples, one for each of the subpopulations of interest, D and D'. To distinguish between these two kinds of populations and samples, we use m's, p's, and a's for the D subpopulation (as we have done in Section 2) and n's, q's, and b's for the D' subpopulation; that is, for the D' population, the data are represented by $(n_{.1},n'_{.1},n_{11},n_{22})$; the parameters, by Q, q_1, and q_2 [or equivalently by $(q_{11},q_{12},q_{21},q_{22})$]; and the prior parameters, by $(b_{11},b_{12},b_{21},b_{22})$. Hence, it is enough to replace n's for m's, N's for M's, q's for p's, Q's for P's, and b's for a's in Section 2 to obtain analogous results for the D' population. We also could construct similar influence diagrams (Figs. 1–3) to obtain the predictions for the D' population.

The novelty here, since the interest is in a new patient who comes to the clinic, is that the number of untested population units (of interest) is one; i.e., either $\{M = 1,N = 0\}$ or $\{M = 0,N = 1\}$. Recall that in the beginning we do not know whether the new patient has D or D'. Also, note that $Bb(1;\alpha,\beta)$ is the Bernoulli distribution with probability parameter $\alpha/(\alpha + \beta)$; i.e., $Bb(1,\alpha,\beta) = Ber\ (\alpha/(\alpha + \beta))$.

Consider now the following indicators, related to the new patient:

$$d = \begin{cases} 0 & \text{if the new patient has } D';\{M = 0;N = 1\} \\ 1 & \text{if the new patient has } D;\{M = 1;N = 0\}. \end{cases}$$

$$t_1 = \begin{cases} 0 & \text{if the result for the new patient is negative in the first test and} \\ 1 & \text{if the result for the new patient is positive in the first test.} \end{cases}$$

and

$$t_2 = \begin{cases} 0 & \text{if the result for the new patient is negative in the second test and} \\ 1 & \text{if the result for the new patient is positive in the second test.} \end{cases}$$

To relate the results of the present article with the ones of Pereira [4], we let $m_{.1}=x$ and $n_{.2} = y$ in Table I.

The results of Section 2 permit us to write the conditional predictive distributions of t_1 given d and of t_2 given t_1 and d as follows:

$$t_1|d \sim \begin{cases} Bb(1;n_{.1} + b_{.1},n_{.2} + b_{.2}) = Ber\left(\dfrac{n_{.1} + b_{.1}}{n + b_{..}}\right) & \text{if } d = 0 \\ Bb(1;m_{.1} + a_{.1},m_{.2} + a_{.2}) = Ber\left(\dfrac{m_{.1} + a_{.1}}{m + a_{..}}\right) & \text{if } d = 1\,. \end{cases}$$

$$t_2|(t_1,d=0) \sim \begin{cases} Bb(1; n_{12}+b_{12}, n_{22}+b_{22}) = Ber\left(\dfrac{n_{12}+b_{12}}{n'_{.2}+b_{.2}}\right) & \text{if } t_1 = 0 \\ Bb(1; n_{11}+b_{11}, n_{21}+b_{21}) = Ber\left(\dfrac{n_{11}+b_{11}}{n'_{.1}+b_{.2}}\right) & \text{if } t_1 = 1\,. \end{cases}$$

$$t_2|(t_1,d=1) \sim \begin{cases} Bb(1; m_{12}+a_{12}, m_{22}+a_{22}) = Ber\left(\dfrac{m_{12}+a_{12}}{m'_{.2}+a_{.2}}\right) & \text{if } t_1 = 0 \\ Bb(1; m_{11}+a_{11}, m_{21}+a_{21}) = Ber\left(\dfrac{m_{11}+a_{11}}{m'_{.1}+a_{.1}}\right) & \text{if } t_1 = 1\,. \end{cases}$$

Considering a priori the simplest Dirichlet distributions, i.e., $a_{ij} = b_{ij} = 1$, $j,i = 1,2$, and using all the data in Table I, we can write

$$Pr\{t_1 = 1|d\} = \frac{47}{54}d + \frac{13}{54}(1-d) \quad \text{and}$$

$$Pr\{t_2 = 1|d,t_1\} = \frac{29}{42}dt_1 + \frac{2}{7}d(1-t_1) + \frac{3}{13}(1-d)t_1 + \frac{3}{39}(1-d)(1-t_1)\,.$$

To complete our formulas, we have the following posterior probabilities, where δ is the prior probability that $d = 1$:

$$Pr\{d = 1|t_1 = 1\} = \frac{\frac{47}{54}\delta}{\frac{47}{54}\delta + \frac{13}{54}(1-\delta)} = \frac{47\delta}{47\delta + 13(1-\delta)} \quad \text{and} \tag{1}$$

$$Pr\{d = 1|t_1 = 0\} = \frac{\frac{7}{54}\delta}{\frac{7}{54}\delta + \frac{41}{54}(1-\delta)} = \frac{7\delta}{7\delta + 41(1-\delta)}\,.$$

$$Pr\{d = 1|t_1 = 1, t_2 = 1\} = \frac{1363\delta}{1363\delta + 126(1-\delta)}\,, \tag{2}$$

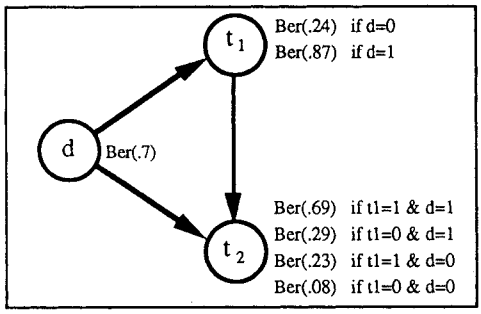

FIG. 4. Influence diagram representing the doctor's information model for the new patient with biliary obstruction.

$$Pr\{d = 1|t_1 = 1,t_2 = 0\} = \frac{611\delta}{611\delta + 420(1 - \delta)},$$

$$Pr\{d = 1|t_1 = 0,t_2 = 1\} = \frac{2\delta}{2\delta + \frac{41}{13}(1 - \delta)},$$

and $$Pr\{d = 1|t_1 = 0,t_2 = 0\} = \frac{5\delta}{5\delta + \frac{492}{13}(1 - \delta)}.$$

Figures 4–6 are the influence diagrams related to the above calculus. Here, we consider $\delta = Pr\{d = 1\} = 0.7$, representing the doctor's opinion about the new patient, before the test results.

Note that, depending on the combined results of the tests, the probability of the quantity of interest, d, can change dramatically. Depending on the costs of misdiagnosis and of wrongful treatment, follow-up procedures may depend

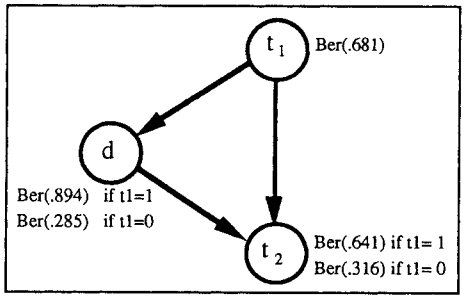

FIG. 5. Influence diagram representing the doctor's information model for the new patient with biliary obstruction, after the observation of the first test results.

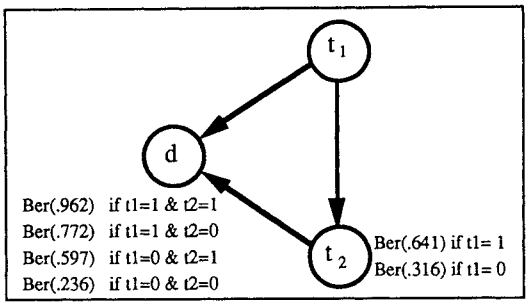

FIG. 6. Influence diagram representing the doctor's information model for the new patient with biliary obstruction, after the observation of the two tests results.

strongly on the test results. Clearly, follow-up procedures may also depend on the doctor's prior opinion, $\delta = Pr\{d = 1\}$. To evaluate the quality of the tests results, we consider various cases and calculate the difference between the posterior and the prior probability of d for all possible values of its prior probabilities. Consider then the functions $f_{(1,1)}(\delta), f_{(1,0)}(\delta), f_{(0,1)}(\delta)$, and $f_{(0,0)}(\delta)$ defined as $f_{(i,j)}(\delta) = Pr\{d = 1 | t_1 = i, t_2 = j\} - \delta$, for $i,j = 0,1$. Also, let $f_{(i,.)}(\delta) = Pr\{d = 1 | t_1 = i\} - \delta$, for $i = 0,1$. Figure 7 presents these six functions showing

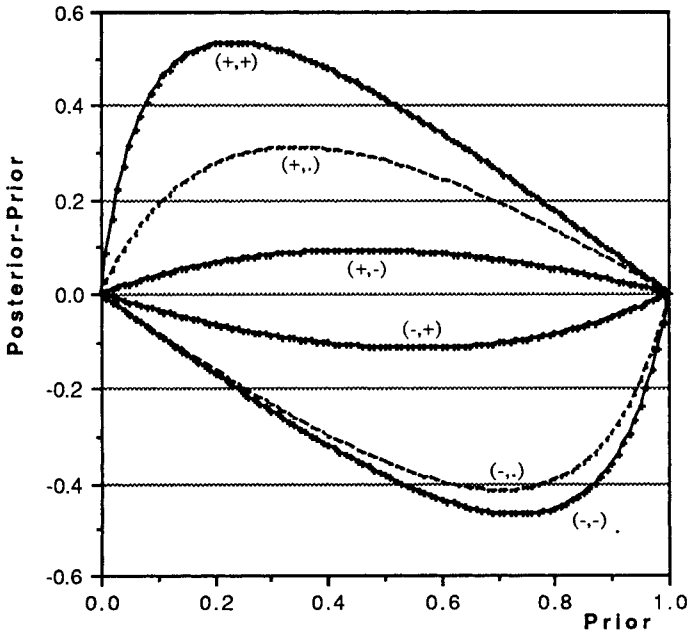

FIG. 7. Change in the probability, due to test results, of a patient belonging to D. The first (2nd) sign is the result of the first (2nd) test. To indicate the curve corresponding only to the first test, we use a "." for the 2nd sign.

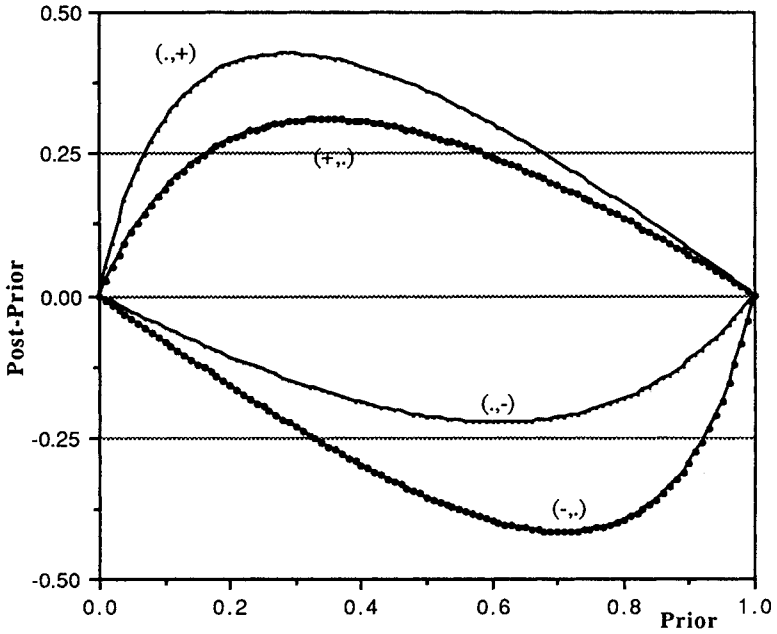

FIG. 8. Change in the probabilities due to results of one test only. We use a "." for the missing result.

for each choice of prior, δ, which test result produces the greatest change from prior to posterior. Figure 8 presents functions $f_{(i,.)}(\delta)$ and $f_{(.,j)}(\delta) = Pr\{d = 1|t_2 = j\} - \delta$, for $i,j = 0,1$. The differences in probabilities as a measure of "test quality" is a surrogate for value of information in the absence of utility information. Comparison of these two figures suggests that the first (second) test is better than the second (first) test for $D'(D)$.

4. SUMMARY

We have shown how test data such as that given in Table I can be used to "calibrate" a test procedure. Using (conservative) Dirichlet priors, we are able to make use of all the previous test data even though some test results are missing. The formulas in (1), Section 3, give the updated (calibrated) probabilities of disease for a new patient given only the first test result. The formulas in (2), Section 3, give the updated (calibrated) probabilities of disease for a new patient given the results from two tests.

As Figures 7 and 8 (based on Table I) show, a test on a new patient can be very informative in the absence of strong prior information if the test is well calibrated.

ACKNOWLEDGEMENT

This research was partially supported by the US Air Force Office Scientific Research (AFOSR-81-0122) to the University of California at Berkeley and CNPq, Brasilia, Brazil, under contract #20771/85-MA. We would also like to acknowledge the help of an excellent referee.

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Received January 1990
Accepted March 1990