

THE VALUE OF LATENT CLASS ANALYSIS IN MEDICAL DIAGNOSIS

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SUMMARY

Assessment of the value of diagnostic indicators such as symptoms and laboratory tests results from calculation of the sensitivity and specificity of the indicators. Knowledge of the rate of occurrence of the disease allows for additional calculations of the error rates in using an indicator. These calculations are accurate only when the data on which they are based are reliable. If the diagnosis, which is used as the criterion for computing the sensitivity and specificity, is not accurate, then the resulting calculations will be in error. We show how a statistical method, latent class analysis, allows for the estimation of the characteristics of indicators even when an accurate diagnosis is unavailable. In addition, the method deals with several indicators at once, and provides a way to combine the information from all the indicators to make a diagnosis.

KEY WORDS Diagnosis Latent class analysis

A pervasive problem in interpretation of the results of indicators of disease (a term we use throughout this paper to refer to symptoms, signs and clinical tests) is their imperfection in pinpointing the true diagnosis. Galen and Gambino¹ described some methods for dealing with this problem when they discussed the influence of rate of false positives, rate of false negatives, and incidence of the disease on the utility of such indicators in making diagnoses. In this paper we suggest a statistical technique to improve upon these methods, namely latent structure (or class) analysis. Goodman,² Clogg,³ and others have established a sound statistical and computational ground for the technique.

Galen and Gambino discuss *sensitivity* (the probability that an indicator is positive when a particular disease is present), *specificity* (the probability that an indicator is negative when a particular disease is not present), *efficiency* (the total probability of making a correct statement about the presence or absence of a particular disease) and *predictive value* (the probability that a person positive for an indicator actually has a particular disease). Calculation of these statistics, however, depends on knowledge of whether each patient in a study actually does or does not have the disease. Error in this determination leads to inaccuracies in the above quantities. In those cases where one cannot determine the correct diagnosis, one must use methods such as latent class analysis. Latent class analysis will, in addition, test the validity of the diagnosis even when the diagnosis is presumed correct. In this paper, we use data from Galen and Gambino on myocardial infarction (MI) to demonstrate the principles involved.

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LATENT CLASS ANALYSIS

Latent class analysis is based on the assumption that the observed categorical indicators are imperfect measures of an unobserved underlying (latent) structure which we can discover and validate with the use of statistical techniques. We hypothesize that the observed relationships result from the existence of two or more classes (types) of people. Within each class, the variables are independent—the observed relationships among the variables occur with combination of the classes. We can then say that the classes explain the observed relationships, since when we hold class constant (i.e. when we examine any one class), the relationships disappear.

In the present case the model of interest is the simplest possible latent class model. The hypothesis is that there are two latent classes (those with and those without MI), and the diagnostic criteria are (possibly imperfect) indicators of the class to which a patient belongs. Such a model has two types of parameters (unknown quantities to be estimated). First, there are the unconditional probabilities that a person is in each of the latent classes. These values depend on the manner of selection of the sample; different samples might show a higher or lower proportion of patients who actually had MI. The second type of parameter is the conditional probability that a person is positive for a particular indicator, given that the person is in a particular latent class. For example, if a person actually has had MI, what is the probability that he or she has a positive CPK-MB test?

From the assumption of conditional independence given latent class, one can easily compute the joint probabilities of observed response patterns and class membership. Summing over classes gives the predicted observed values. Assuming a multinomial distribution of the observed values leads easily to the use of any of several procedures for maximum likelihood estimation of the parameters. A detailed discussion of one such approach is by Goodman;² this method is implemented in the computer program MLLSA by Clogg.³

After estimation of these parameters for a specified model, the next step is to determine the plausibility of the hypothesized model. There may be three or more classes—for example, those without MI, those with mild MI and those with severe MI—or a latent class model may be inappropriate for certain data. Given the parameter estimates obtained in the analysis, one can compute expected frequencies of each pattern of response on the indicators and compare these with the observed frequencies. If the expected and observed frequencies agree closely (as measured by a chi-square test of goodness of fit), then the data are consistent with the model.

If we find no model consistent with the data, then we must query the correctness of the assumption that there are distinct categories. If we find only one model consistent with the data, then our degree of belief in that model increases considerably. If more than one model fits well, then (under some circumstances) we can compare the fit of the models and, if we find no differences, we can retain the simpler model. (One complication is that sample size will determine the power of the statistical tests. With small sample sizes we may have difficulty rejecting incorrect models, whereas with large sample sizes we may find that no model fits well.) If the models which fit are not special cases of one another, then we cannot compare them directly, but must judge them on other criteria, such as scientific plausibility and utility.

Once we select a model as best for a particular use of a data set, then we can interpret the parameters and make further useful calculations. The following sections demonstrate the interpretation for the MI data set.

DATA ON MYOCARDIAL INFARCTION

The data analysed here (Table I) are from Table 5 of Reference 1, and pertain to a study of patients in the Coronary Care Unit of The Presbyterian Hospital in New York City. The patients were

Table I. Data, expected values and assignment to latent classes based on two-class model

Q-wave	Indicator			Frequencies		Class	Probability of correct classification
	History	LDH	CPK	Observed	Expected		
yes	yes	yes	yes	24	21.62	2	1.000
no	yes	yes	yes	5	6.63	2	0.992
yes	no	yes	yes	4	5.70	2	1.000
no	no	yes	yes	3	1.95	2	0.889
yes	yes	no	yes	3	4.50	2	1.000
no	yes	no	yes	5	3.26	1	0.580
yes	no	no	yes	2	1.19	2	1.000
no	no	no	yes	7	8.16	1	0.956
yes	yes	yes	no	0	0	—	—
no	yes	yes	no	0	0.22	1	1.000
yes	no	yes	no	0	—	—	—
no	no	yes	no	1	0.89	1	1.000
yes	yes	no	no	0	0	—	—
no	yes	no	no	7	7.78	1	1.000
yes	no	no	no	0	0	—	—
no	no	no	no	33	32.12	1	1.000

The probabilities of correct classification cannot be computed for cells with expected values of zero, and are left blank. Also, the class to which these people should be assigned is undetermined.

The observed frequencies are from Galen and Gambino.¹

admitted for the purpose of ruling out myocardial infarction (MI). Each of 94 patients had the following information available: (i) presence or absence of a positive new Q-wave in the ECG, (ii) presence or absence of a classic clinical history, (iii) presence or absence of high CPK-MB, (iv) whether or not the patient had flipped LDH and (v) the final clinical diagnosis based on the clinical history and ECG only. (For more detail on these data, see the original source.) The data used for the latent class analysis consist of the first four of the above five variables.

ANALYSIS OF MYOCARDIAL INFARCTION DATA

The first step in the analysis is to establish that there are actually relationships among the variables. With no relationships among the observed variables, there cannot be more than one latent class. For the myocardial infarction data, the test of independence among the four variables produces a likelihood ratio chi square value of 149.47 with 11 d.f., indicating that there are relationships among the variables.

The next step is to test the two-class model. The chi-square test of goodness of fit is 4.29 with 8 d.f.; the small chi-square value indicates that we cannot reject the model; consequently it is plausible. (We would normally have 6 d.f. for testing this model; there are 8 here because of the location of the observed zero frequencies in the data.) Before we accept the model, we might try other plausible models, since more than one model may fit the data. One model we would normally test is a three-class model; here it is unnecessary, because the small chi-square for the two-class model indicates that we would find no improvement with the more complicated three-class model.

A larger sample would allow a better test of the model; a sample of less than one hundred may be too small to detect possible lack of fit of a two-class model. One indication that the power of the statistical tests of these models is reasonably high, however, is that we did reject some models. For instance, we rejected the model of independence, as well as a model discussed below.

Table II. Parameter estimates for two-class model

	Class	
	1	2
Unconditional class probabilities	0.542	0.458
Conditional probabilities of indicators, given latent class		
Positive Q-wave	0.000	0.767
Classic history	0.195	0.791
Flipped LDH	0.027	0.828
High CPK	0.196	1.000

Another plausible model is that there is a class of MI patients among whom all are positive on all the indicators, a class of patients without MI among whom all are negative on all the indicators, and another group of patients 'in-between' these classes among whom some are positive for some indicators but not others. Quasi-independence models can test such theories. In this case, we construct a model in which we assume that independence of indicators holds among those who do not have consistent response profiles. A statistical test of this quasi-independence model for the MI data gives a chi-square of 18.32 with 9 d.f. Since this is a large chi-square value, we reject the quasi-independence model.

Apparently there are no other simple latent class models which would account for the relationships in these data; hence we accept the two-class model. The parameter estimates for this model appear in Table II. The conditional probabilities indicate, for example, that those in latent class 1 have a probability of zero of having Q-waves, whereas those in latent class 2 have a probability of 0.77 of having Q-waves. The conditional probabilities for the other indicators show a similar pattern, with class 1 having low probabilities of being positive for the indicators, and class 2 having high probabilities. This establishes class 1 as the class without MI, and class 2 as the class with MI.

The conditional probabilities show that what would be (if we had used an external criterion) the sensitivity and specificity of the individual indicators. For example, Q-waves have a sensitivity of 0.77 for MI, and a specificity of 1.0 for MI. The highest sensitivity is for CPK (1.00, or 100 per cent), and the sensitivities of the other three tests are moderately high. The highest specificities are for Q-waves (1.0) and LDH (0.97). Note that, whereas Galen and Gambino could not really establish the sensitivity and specificity of Q-waves and history (since these were used to make the diagnosis), we have no such restrictions because we did not employ the diagnosis as a criterion.

The unconditional probabilities of being in each latent class were 0.54 for class 1 (no MI) and 0.46 for class 2 (MI). These values, unlike the conditional probabilities, depend on the composition of the sample. Their only significance is for predicting these probabilities in samples analogous to that above, which consisted of all patients admitted to the coronary care unit of a particular hospital to exclude MI as a diagnosis. It may be of some use to know that of such patients, about half will have MI and half will not. This establishes the base rate for computation of efficiency, predictive value and other measures of utility of the indicators.

Although the calculation of the sensitivity and specificity of indicators is useful, a primary purpose of the analysis is to provide guidance in classification of patients as either having or not having MI. To do this, we can use the conditional and unconditional probabilities in a formula related to Bayes' theorem to find, for any pattern of indicators, the probability that a person with that pattern is in a particular latent class. With equal gravity for each of the two possible types of

errors (false diagnosis of MI; failure to diagnose MI when present) we could classify people into the most likely category given their particular symptoms. Table I shows the observed and expected cell frequencies, the latent class for each observed response pattern (given equal gravity of each type of error) and the probability of correct classification. There is doubt for only one cell. A person with classic history and high CPK, but without positive Q-waves or flipped LDH is classified as having MI, but the probability of an error is 0.42. In samples like that studied, we expect about three per cent of the sample to show this pattern of indicators ($3.26/94 = 0.0347$). For most patients, however, we have considerable certainty about whether or not they had MI.

Because latent class analysis does not use the final diagnosis of the physician, it has use as an independent check on the physician's diagnosis. In general, the results of the latent class analysis agree with the final clinical diagnosis and with the conclusions of Galen and Gambino. For patients positive only for CPK, the latent class analysis indicates a high probability of no MI. In the clinical diagnosis, of the seven patients with this pattern of indicators six were judged not to have MI. Galen and Gambino disagree with these results: they argue that the high sensitivity of CPK indicates that the patients should be treated for MI. Their analysis, however, indicated a higher specificity for CPK than did the latent class analysis.

Although the calculations performed here assume equal gravity of false positives and false negatives, adjustment for differential seriousness is a simple matter. The adjustment merely changes the cut-off probability for declaring a person to have MI from 0.50 to a higher number (if a false positive is the more serious error) or a lower number (if a false negative is the more serious error).

In addition to determining the characteristics of each indicator individually, latent class analysis results have use in assessment of the utility of various combinations of indicators in the diagnosis of disease. For instance, one might wish to know the utility of the two lab tests, CPK and LDH, without the clinical history and information from the ECG. We first use Bayes' theorem to determine the utility of each of the two tests individually. (In the calculations which follow, we assume that the base rate of MI is 0.458, as in the sample.) If LDH is positive, there is a probability of 0.96 of MI; if it is negative, the probability of MI is 0.13. For CPK, the corresponding probabilities are 0.81 and 0.0. With both tests together, there are four combinations of presence and absence of the symptoms. With both tests positive, the probability of MI is close to 1; with CPK negative (regardless of whether or not LDH is positive), the probability of MI is close to zero. If, however, LDH is negative and CPK is positive, then the probability of MI is 0.43; the diagnosis in this case is very uncertain. With only these two tests, there will be a high error rate when this particular result occurs, which would happen in just under one-fifth of all cases. In this case, CPK has insufficient specificity to conclude occurrence of MI, whereas LDH has insufficient sensitivity to establish the absence of MI.

To summarize the effects of use of both tests versus either one alone, Table III shows the expected number of false positives and false negatives for 10,000 cases using LDH only, CPK only and both LDH and CPK. We computed these values using Bayes' theorem, and again assumed the same base rate as in the sample. Use of both tests reduces the rate of false positives, especially compared with CPK alone. Use of both tests, however, does not decrease the rate of false negatives.

WHEN THE TWO-CLASS MODEL DOES NOT FIT

Although the two-class model fits well here, it will not always do so. One possible reason for its failure is the existence of some other disease that has two or more indicators in common with the disease of primary interest. If this happens, then that set of variables will lack conditional

Table III. Error rates using CPK and LDH
(per 10,000 cases)

	False positives	False negatives
LDH alone	146	788
CPK alone	1060	0
LDH and CPK	29	788

independence even within latent classes of the disease of primary interest. This will cause rejection of the two class model even when there are two classes as far as the primary disease is concerned. One must then include more classes (and possibly additional indicators) to distinguish those who have the primary disease, those who have the secondary disease, those who have both and those who have neither. One can easily specify and test such models.^{2,4} In these cases, it is best to find at least two indicators for each disease that are specific for that disease, but not for the other. We shall not demonstrate these models here.

One problem with traditional methods is their assumption of two kinds of people; those with and without the disease. In fact, as noted earlier, there may be three or more categories, or a continuum model of the disease may apply. Use of latent class methods will allow the researcher to determine which is true. Fit of a two-class model justifies computation of sensitivity, specificity, etc. in the manner described above. Fits of more complicated models lead to more complicated procedures in practice, even when the theory is known. Traditional methods deal primarily with a disease/no-disease dichotomy.

COMBINING INDICATORS: CONDITIONAL INDEPENDENCE

One criticism by Bayesian methods (closely related to this parametrization of latent class analysis) is that use of information from more than one indicator requires that they be unrelated (statistically independent). In the case of latent class models, this is not true; the important criterion is that the indicators are *conditionally* independent, given latent class membership. But this is true by definition of the latent class model and its assumptions. As long as one has the conditional probability of displaying each indicator as a function of latent class, as well as the unconditional probability of belonging to each class, then one can compute in a straightforward manner the probability of being in a particular latent class, with any given combination of indicators (using Bayes' theorem). Since the latent class model produces the necessary probabilities, the application is straightforward.

When, however, we do not use latent class methods we have a problem when we are uncertain of perfect diagnosis of the criterion disease. We have already indicated that, when the diagnosis is faulty, we cannot estimate the specificity and sensitivity correctly. But in addition, we may have bias in the estimate of the unconditional probability of having the disease under these conditions, thus making the application of Bayes' theorem even more problematic. Even with these potential problems, there is evidence for conditional independence. Diamond and Forrester⁵ studied four indicators of coronary artery disease, and found independence among those with the disease. Patients without the disease were of insufficient number to determine whether independence held in that group.

CONCLUSION

When the diagnosis in question is not subject to appreciable error, then the methods suggested in the literature are adequate to calculate sensitivity, specificity, and related measures of the quality of clinical tests. However, with appreciable error in the diagnosis, we need methods such as latent class analysis to provide the required information. Latent class analysis also has use when the criterion disease is thought to be accurately diagnosed; if this is correct, then the results of the latent class analysis should agree with the results of traditionally recommended methods.

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