Bayesian methods and decision making in glaucoma

Niro Kasahara, MD
Glaucoma Service and Ophthalmic Epidemiology & Statistics Service, Department of Ophthalmology, Santa Casa de Sao Paulo School of Medical Sciences, Irmandade da Santa Casa de Misericordia de Sao Paulo, Sao Paulo, Brazil.

Correspondence address:
Niro Kasahara, MD
Rua Sao Mauro, 292 Sao Paulo – SP – 02526-050 Brazil
Fone: (55 11) 4195-3406
Email: nirokasahara@ig.com.br
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Abstract
This article reviews the Bayesian statistical approach to diagnostic test analysis and application in the management of glaucoma patients. The central idea of the Bayesian method is the use of study data to update the state of knowledge about a quantity of interest. In diagnostic test analysis, the Bayesian approach explicitly elicits a clear interpretation of chances of a particular eye disease given a positive test result. The Bayesian method also provides a reasonable rationale for deciding whether to perform a laser iridotomy in a patient with occludable angles. We present several literature examples of Bayesian methods in practice, especially as it relates to glaucoma evaluation and progression.

Introduction
Bayes’ theorem is a procedure for revising and updating the probability of some event in the light of new evidence. It originated in an essay presented to the Royal Society of London for Improving Natural Knowledge by Reverend Thomas Bayes and published post mortem by his peer Richard Price in 1763.

The Bayesian method is an approach to inference based on Bayes’s theorem, in which prior knowledge in the form of a specified probability distribution for the unknown parameters (prior distribution) is updated in the light of observed data to give a revised probability distribution for the parameters (posterior distribution). This form of inference differs from the classical form of frequentist inference in several respects, particularly in the use of a prior probability distribution for the parameters. The prior distribution represents the investigators’ knowledge before collecting data. The method can relate the chance that an event A happened given the indicator X, or mathematically, P(A | X), as well as P(X | A), the chance the indicator X happened given that event A occurred.

Bayesian inference has found application in a range of fields including computer science (anti-spam email filtering, artificial intelligence and expert systems), engineering, philosophy, marketing (pricing decision, promotional campaign, logistic of distribution), medicine and law (to coherently accumulate the evidence for and against a defendant). In brief, this article will discuss the clinical application of the Bayesian method in diagnostic testing for eye disease and focus on its use in glaucoma research and patient management.

Clinical example: anatomy of a test*
Consider a hypothetic eye condition with 1% prevalence in the population. The diagnostic test can detect up to 80% of cases (real positive) and miss up to 20% (undetected disease). Conversely, the same diagnostic test gives 10% false positive results (so, 90% correctly return a negative result). Plotting these data on Table 1, one can easily notice that if the patient has the disease (first column) there is 80% chance he will test positive and 20% chance he will test negative. Healthy subjects are in the second column. They have 10% chance of being tested positive, and 90% chance of being tested negative.

Consider a patient with a positive test result. What are the real chances that he has the eye disease? If he was tested positive, he can either be a true positive or a false positive (first row of Table 1). At this point, it is wise

not make any assumption. The chance of a true positive is given by the product of the chance he has the eye disease times the chance test detected it (1% x 80% = 0.008). The chance of a false positive is calculated multiplying the chance he does not have the eye disease by the chance the test detected it anyway (99% x 10% = 0.099). Placing those figures on Table 2 facilitates the understanding.

The chances that a patient with positive test result definitively has the disease can be estimated by simple probability formulae. The chance of an event is the number of ways it could happen given all possible outcomes (probability = desired event ÷ all outcomes). In the example, the chance of getting a real, positive result is 0.008. The chance of getting all positive result is the chance of a true positive plus the chance of a false positive (0.008 + 0.099 = 0.107). Hence, the chance of eye disease is 7.4% (0.008 ÷ 0.107 = 0.074).

Unexpectedly, the real chance that a patient with positive test result definitively has the disease is very low (7.4% chance of disease, rather than the supposed accuracy of the test of 80%). However, when we analyze this figure on population grounds it seems more logical. The test gives a false positive 10% of the time, so that in a given population there will be a large number of false positives, to such an extent that most of the positive test results will be incorrect.

**Clinical example: Bayes’ theorem**

What are the real chances that a patient with a positive test result has the eye disease? One can answer the question using the Bayes’ theorem. The theorem allows one to take the test results and correct for the “skew” introduced by false positives getting the real chance of having the event. It imprints the actual probability of an event given the measured test probabilities. Assuming one knows the real probabilities and the chances of false positive and false negative, adequate correction for measurement errors can be made. The equation is:

\[
P(A \mid X) = \frac{P(X \mid A) \cdot P(A)}{P(X \mid A) \cdot P(A) + P(X \mid \neg A) \cdot P(\neg A)}
\]

Where:

\[
P(A \mid X)\text{ is the chance of having eye disease (A) given a positive test (X). This is the answer to the question;}
\]

\[
P(X \mid A)\text{ is the chance of a positive test (X) given that the patient has the disease (A) or the chance of a true positive (80%);}
\]

\[
P(A)\text{ is the chance of having the disease (1%);}
\]

\[
P(X \mid \neg A)\text{ is the chance of a positive test (X) given that the patient does not have the disease (\neg A) or the chance of a false positive (10%); and}
\]

\[
P(\neg A)\text{ is the chance of not having the disease (99%).}
\]

The equation can be further simplified when one realizes that it amounts to the chance of a true positive result divided by the chance of any positive result.

\[
P(A \mid X) = \frac{P(X \mid A) \cdot P(A)}{P(X)}
\]

In the algorithm, Pr(X) is a normalizing constant and it helps to scale the equation. This factor corrects the false belief that a positive test result gives an 80% chance of having the eye disease. Besides, Pr(X) conveys the chance of getting any positive result, both true positive and false positive, serving as a weighted average. In the example, Pr(X) is very large because of the potential for false positives.

Ideally, if a diagnostic test were completely accurate, the test probabilities and real probabilities corresponded to each other. In clinical practice, however, diagnostic tests do give false positive results in healthy subjects and fail to detect disease in affected patients. Bayes’ theorem allows one to look at the skewed test results and correct for errors, recreating the original population and finding the real chance of a true positive result.

**Clinical applications in glaucoma**

Bayesian statistics have been extensively used in glaucoma research with especial interest in disease diagnosis and progression analysis.

In order to determine whether an unsupervised machine learning classifier...
can identify patterns of visual field loss that are consistent with typical patterns learned by decades of human experience. Sample et al evaluated standard perimetry thresholds plus age from patients with glaucoma and healthy subjects clustered with an unsupervised machine classifier, variational Bayesian mixture of factor analysis (vbMFA). Without training-based diagnosis (unsupervised learning), the vbMFA identified four important patterns of field loss in eyes with glaucomatous optic neuropathy in a manner consistent with years of clinical experience.

Jansonius estimated the specificity of a clinical evaluation of a series of visual fields and calculated the positive predictive value of progression using Bayes’s theorem. The author concluded that the realistic series of visual fields that were apparently progressive had a positive predictive value of typically 0.5, i.e., half of them were stable. In the case of a high prior probability (uncontrolled glaucoma or long interval between successive fields), four fields may suffice to diagnose progression, whereas at least six fields were required if the prior probability was low.

Progressive loss of the field of vision is characteristic of a number of eye diseases such as glaucoma. Recently, there has been an explosion in the amount of data being stored on patients who suffer from visual deterioration including field test data, retinal image data and patient demographic data. However, there has been relatively little work in modeling the spatial and temporal relationships common to such data. Tucker et al introduced a novel method for classifying visual field data that explicitly models these spatial and temporal relationships. The authors used a spatio-temporal Bayesian classifier and compared it to a number of classifiers from the machine learning and statistical communities. The authors concluded that the results outlined in the study paved the way for a substantial program of study involving many other spatial and temporal datasets, including retinal image and clinical data.

Intraocular pressure (IOP) fluctuation over 24 hours is an independent risk factor for glaucoma progression, however, nighttime IOP measurement is not routine practice. Using a Bayesian network (BN), Nordmann and Berdeaux assessed the likelihood of a nighttime IOP peak >18 mm Hg based on daytime measurements. The authors concluded that daytime IOP measurements were highly intercorrelated. According to this BN, IOP at 12:00 and 20:00 hours were more strongly associated with the nighttime IOP peak than other IOP measurements. BN can estimate the risk of a nighttime IOP peak >18 mm Hg. Daytime IOP control was important for nighttime IOP control.

Zhu et al developed a method for predicting visual function from retinal nerve fiber layer (RNFL) structure in glaucoma. RNFL thickness measurements from scanning laser polarimetry (SLP) and visual field (VF) sensitivity from standard automated perimetry were made available for 535 eyes. In a training dataset, structure-function relationships were characterized by using linear regression and a type of neural network: radial basis function customized under a Bayesian framework (BRBF). These two models were used in a test dataset to predict sensitivity at individual VF locations from RNFL thickness measurements and predict the spatial relationship between VF locations and positions at a peripapillary RNFL thickness measurement annulus. Predicted spatial relationships were compared with a published anatomic structure–function map. The BRBF generated clinically useful relationships that related topographical maps of RNFL measurement to VF locations and allowed the VF sensitivity to be predicted from structural measurements.

In an observational cohort study, Medeiros et al presented and evaluated a Bayesian hierarchical model to integrate information from the longitudinal measures and classify individual eyes as progressing or not. Estimates of sensitivity and specificity of the Bayesian method were compared with those obtained by the conventional approach of ordinary least squares (OLS) regression. The Bayesian hierarchical modeling approach for combining functional and structural tests performed significantly better than the OLS method for detection of glaucoma progression.

In an observational cohort study with 357 glaucoma patients, Medeiros et al created a hierarchical Bayesian model to incorporate results from the Guided Progression Analysis in the prior distribution for the visual field index slopes, allowing the event-based method to influence the inferences made for the trend-based assessment and compared with the conventional ordinary least squares (OLS) regression method of trend-based assessment. The Bayesian hierarchical modeling approach for integrating event-
and trend-based assessments of visual field progression performed better than either method used alone. Estimates of rates of change obtained from the Bayesian model had increased precision and may be superior to the conventional OLS method for providing information on the risk of development of functional impairment in the disease.10

Russell et al assessed whether neuroretinal rim area (RA) measurements of the optic disc could be used to improve the estimate of the rate of change in visual field (VF) mean sensitivity in patients with ocular hypertension (OHT) using a Bayesian linear regression (BLR), compared to a standard ordinary least squares linear regression (OLSLR) of mean sensitivity (MS) measurements alone. The authors concluded that BLR provided a significantly more accurate estimate of the rate of change in MS than the standard OLSLR approach, especially in short time series, suggesting that structural measurements could be used successfully in statistical models to assist clinicians monitoring VF progression in patients with OHT.11

Goldbaum et al evaluated the ability of Progression of Patterns (POP) to identify progression of glaucomatous visual field (VF) defects. POP which uses variational Bayesian independent component mixture model (VIM), a machine learning classifier, added to the information available to the clinician for detecting VF progression.12

Bayesian’s inference to decide on laser iridotomy

In a comprehensive review on the subject, Thomas et al exemplified the use of Bayesian inference to decide whether to perform a laser iridotomy in a primary angle closure suspect (PACS).13 The incidence of acute primary angle closure (APAC) in the general population is available, but the information needed is APAC in a PACS. This probability can be calculated using Bayes’ theorem. The APAC usually occurs in PACS or primary angle closure (PAC). In time, some normal subjects can become PACS, so one can make an initial assumption that P (PACS | APAC) is 0.95 (95%). The probability of APAC is 0.00012 per year and the estimate probability is 0.98 (8%).

\[
P(\text{APAC} | \text{PACS}) = P(\text{PACS} | \text{APAC}) \cdot P(\text{APAC}) / P(\text{PACS}) = 0.95 \times 0.00012 / 0.08 = 0.00142 \text{ or 14 per 10,000 PACS per year.}
\]

Assuming that P (PACS | APAC) is 99%, this calculation becomes 0.00014 or 14 per 100 000 PACS per year. Using the reported rate of APAC in those over 60 years of age, the rate of APAC in PACS over 60 years of age can be calculated as 1%. Clearly if we perform iridotomies for all PACS a great number of patients will have unnecessary procedures. The use of Bayes’ theorem allows practitioners to make reasonable clinical decisions.13

Conclusion

In summary, the Bayesian’s method is the use of study data to update the state of knowledge about a quantity of interest. In diagnostic test analysis, the Bayesian approach explicitly elicits a clear interpretation of chances of a particular eye disease given a positive test result. The Bayesian method also provides a reasonable rationale for deciding whether to perform a laser iridotomy in a patient with occludable angles. The clinical utility of Bayes’ theorem is dependent on a knowledge of and access to relevant valid literature. It imparts the actual probability of an event given the measured test probabilities and increases the chances of certainty.

REFERENCES