A Bayesian Prediction Model of Severe Intra-ventricular Hemorrhage in Very Pre-Term Infants

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Abstract

Nearly 20% of very preterm infants (gestational age < 32 weeks) will experience severe intra-ventricular hemorrhage (IVH stage 3 or 4)(Stoll 2010). Prophylactic use of indomethacin has been shown to reduce the risk of severe IVH but this intervention's side effects require its judicious use on only those infants at the greatest risk of severe IVH. Current research suggests infants with increased cerebral oxygenation may be at greater risk of severe IVH (Noori 2013) and neonate cerebral sensors can easily and continuously measure this biometric resulting in high dimensional data sets. In this work we employ a Bayesian prediction model on the cerebral tissue oxygenation index (c-TOI) measures of 22 very preterm infants (5 experienced IVH) continuously monitored for 72 hours and evaluate the model's performance via leave-on-out-cross validation at 5, 10, and 12 hours. By constructing conditional densities of this biometric at each time point for both groups of infants we obtain conditional group assignment probabilities that are sequentially updated at each time point. At 12 hours, this model has 80% sensitivity and 82% specificity.

Key Words: Bayesian Methods, Classification, Health Data, Intra-ventricular Hemorrhage, High Dimensional Data, Bayesian Classification

1. Introduction

Very preterm infants, born prior to 32 weeks gestational age, face a host of challenges as their bodies complete the development process that typically occurs in utero. These infants face higher rates of intra-ventricular hemorrhage (IVH), necrotizing enter colitis (NEC), chronic lung disease, sepsis, and other morbidities than their preterm, late preterm, and term counterparts (Volpe 2001, Russel 2007).

Within the lateral ventricles lies a metabolically highly active tissue, the germinal matrix, which is the site where hemorrhage occurs in the immature brain. The immature fragile capillary bed of the germinal matrix is prone to rupture leading to IVH as a result of a host of insults such as ischemia-reperfusion injury.

About 90% of IVH cases happen within the first 72 hours of life and, while an infant with IVH may present with seizure, such hemorrhages are often initially asymptomatic and are often only detected on routine screening by cranial ultrasound. Severity of IVH can range from mild (grade I and II) with no major complications, to severe (grade III and IV) which may result in higher rates of mortality or long term brain injury including hydrocephalus and cognitive disability.

In a large, multicenter study, Stoll et al. (2010) collected data on 9575 very preterm infants from January 1, 2003 to December 31, 2007. Incidence of severe IVH among this population was about 20% overall with decreasing incidence estimates of 38%, 36%, 26%, 21%, 14%, 11%, and 7% for increasing gestational ages of 22, 23, 24, 25, 26, 27, and 28 weeks, respectively (see Figure 1). Clearly, reducing the incidence of IVH and its effects among this population is a major focus of the medical community.

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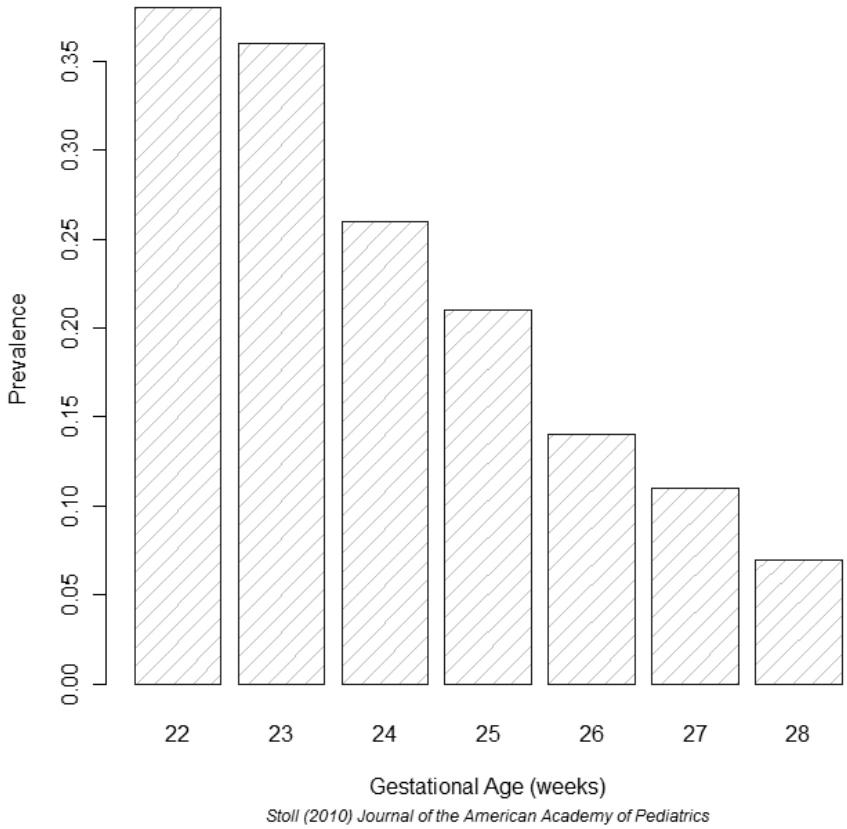

Figure 1: IVH incidence estimates among very preterm infants by gestational age from Stoll et al. (2010).

Once IVH occurs, there are no effective treatments therefore, prevention of IVH is the key in reducing IVH-associated mortality and morbidities. While prophylactic use of inodomethacin has been shown to reduce the incidence of severe IVH in very preterm infants if administered within the first 12-24 hours (Ment 1985, Bada 1989, Schmidt 2001), the lack of improvement in neuro-developmental outcome at 18 months (Schmidt 2001) has resulted in abandoning of this strategy by most neonatologists. The exact reasons for the lack of long-term benefit of prophylactic indomethacin despite a significant reduction of severe IVH, a major risk factor for poor neurodevelopmental outcome, are not known. It is possible that indiscriminate exposure of the whole population to a medication with known adverse effects (including decreased cerebral blood flow) would cancel out the beneficial effect of reducing IVH. Therefore, identifying the very preterm infants at greatest risk for severe IVH and administering prophylactic indomethacin to this selective group rather than to every very preterm infant will likely tip the risk/benefit ratio in favor of this treatment.

It is known that cerebral blood flow (CBF) markedly increases over the first few days after birth (Meek 1998, Kluckow 2000a, Kehrer 2005). Several studies have documented an early ischemic period in preterm infants who later develop IVH (Meek 1999, Kluckow 2000b, Kissak 2004, Sorensen 2008, Verhagen 2010, Noori 2013). Cerebral tissue oxygen (c-TOI) saturation has been shown to be lower in preterm infants who develop IVH compared to those who do not (Sorensen 2008, Verhagen 2010, Noori 2013). Kluckow and Evens showed a rise in superior vena cava flow (a surrogate for CBF) before occurrence of

IVH. Noori et al demonstrated that very preterm infants with low CBF develop IVH only after improvement in cardiac function and increase in CBF.

2. Proposed Prediction Model

Let S_l define the event that a subject belongs to group l for $l = 1, \ldots, s$, let $x^{(1)}, \ldots, x^{(p)}$ be a set of p observations that arise in sequence from that subject, and let $x^{(j)}|S_l$ define the conditional event of observing $x^{(j)}$ given the subject belongs to group l. Further suppose the initial prior probability of belonging to group l is given by $P(S_l^{(0)})$ and conditional probabilities corresponding to the conditional events, $P(x^{(j)}|S_l)$, can be computed. Then the posterior probability of belonging to group l having observed $x^{(j)}$ can be computed as

$$P(S_l|x^{(j)}) = \frac{P(S_l|x^{(j-1)})P(x^{(j)}|S_l)}{\sum_{l=1}^{S} P(S_l|x^{(j-1)})P(x^{(j)}|S_l)} \tag{1}$$

Anderson and Dubnicka (2009) introduce the above sequential naïve Bayes classifier and demonstrate how $P(x^{(j)}|S_l)$ can be obtained when $x^{(1)}, \ldots, x^{(p)}$ are discrete. In this paper, we propose a modification to (1) for use with continuous $x^{(1)}, \ldots, x^{(p)}$ and demonstrate its use and discuss its performance using the c-TOI measures obtained in Noori (2013) to predict very preterm infants at risk of severe IVH.

2.1 Sequential Naïve Bayes Classifier for Continuous Data

Continuous data can be thought of as observations drawn from a population with an unobservable continuous probability density function, $f(x)$. Using observed data $x^{(1)}, \ldots, x^{(p)}$, one can compute a kernel density estimate, $\hat{f}_h(x)$, where $h > 0$ is the bandwidth, a smoothing parameter used in estimating the underlying probability density function, which allows for inference about the population. Clearly, observations are less likely to be drawn from the tales of $f(x)$ then from its higher density areas. This leads us to propose the following modification to 1 in order to define conditional probabilities for use in its computation.

Let $\hat{f}_h(x^{(j)}|S_l)$ be a kernel density estimate of a continuous probability density function $f(x^{(j)}|S_l)$. That is to say $\hat{f}_h(x^{(j)}|S_l)$ is a conditional density estimate of the l^{th} group for the j^{th} observed quantity from a reference data set. Suppose a subject to be classified to a group yields the quantity $x_{new}^{(j)}$. Then

$$P_c(x^{(j)}|S_l) = \begin{cases} \int_{-\infty}^{x_{new}^{(j)}} \hat{f}_h(x^{(j)}|S_l)dx^{(j)} & \text{if } x_{new}^{(j)} < x_{med}^{(j)} \\ \int_{x_{new}^{(j)}}^{\infty} \hat{f}_h(x^{(j)}|S_l)dx^{(j)} & \text{if } x_{new}^{(j)} \geq x_{med}^{(j)} \end{cases}$$

where $x_{med}^{(j)} = x$ such that $\int_{-\infty}^{x} \hat{f}_h(x^{(j)}|S_l)dx^{(j)} = 1/2$. The logic behind the above expression hails from the notion that the observation will lie near the median of conditional density estimates of groups likely to have produced it and in the tails of conditional density estimates of groups less likely to have produced it. Hence the tail areas above or below the median provide reasonable information about the likelihood of the observation given each group under consideration.

Equation (1) can be modified accordingly to produce a sequential naïve Bayes classifier for continuous data of the form

$$P(S_l|x^{(j)}) = \frac{P(S_l|x^{(j-1)})P_c(x^{(j)}|S_l)}{\sum_{l=1}^{S} P(S_l|x^{(j-1)})P_c(x^{(j)}|S_l)} \tag{2}$$

2.1.1 *Smoothing the Posteriors*

Posterior estimates of group assignments resulting from (2) ignore the fact that each observation $x^{(j)}$ is only one of many, possibly thousands, of sequential observations and gives complete control of the posterior to the current observation under consideration. This results in what can be large swings in the direction of the posterior probability from one observation to the next. In order to put each sequential observation into its proper perspective, as one of many observations, we propose smoothing the posterior probability estimates by using an exponential smoothing parameter $0 < \epsilon < 1$ together with the computed conditional density estimate in equation 2.1

$$P(x^{(j)}|S_l) = P(x^{(j)}|S_l) + \left(\left(\frac{P(x^{(j)}|S_1) + \cdots + P(x^{(j)}|S_s)}{s}\right) - P(x^{(j)}|S_l)\right) * \epsilon \quad (3)$$

where $\epsilon = \left(1 - \frac{1}{p}\right)$. The result of (3) is to shrink the movement of each posterior probability so as to produce stable, meaningful posterior probabilities computed in the context of all the data.

2.2 Posterior Probability Plots

A by-product of the sequential naïve Bayes classifier is a sequence plot of the posterior probabilities. Such a plot provides a picture of how the posterior probabilities change over time and could potentially be useful for making real time decisions about treatment interventions. For example. a clinician may use these plots to continuously monitor a subjects real time risk of IVH and incorporate that information along with other considerations to make evidence based care decisions accordingly. Examples of these plots and their potential usage is given in section 3.1.

3. Example

In a study conducted by Noori et al (2013) at the University of Oklahoma Health Sciences Center (OUHSC0) 22 very preterm inborn infants had their cerebral tissue oxygenation index (c-TOI) monitored every 10 minutes over the first 72 hours of life using near infrafed spectroscopy (NIRS). This produced a high dimensional data set with 22 subjects each yielding 421 c-TOI readings as well as other demographic measures. In addition to monitoring c-TOI, subject heart rate and arterial blood flow were also monitored and a trained neonatologist conducted a cranial ultrasound every 12 hours to detect presence and severity of IVH. The proposed sequential naïve Bayes classifier with uniform piors on the two groups ("at risk" and "not at risk") were used to determine whether c-TOI profiles from the subjects with and without IVH could be used to identify subjects at risk of IVH. Also of interest was to investigate how well the proposed classifier performs at various time points, especially those in which interventions might effectively be administered (i.e. before 12 hours).

3.1 Results

Over the 72 hour study period, 5 infants (22.7%) experienced severe IVH. Noori (2013) reports that the mean time to IVH detection was 39.2 hours (95% CI=(31.6,46.8)) and that the c-TOI profiles between the IVH and No IVH groups differed significantly. The proposed sequential naïve Bayes classifier was used to predict each infant's "at risk of severe IVH" status using data observed up to 5, 10, 12, and 72 hours and the classification rate

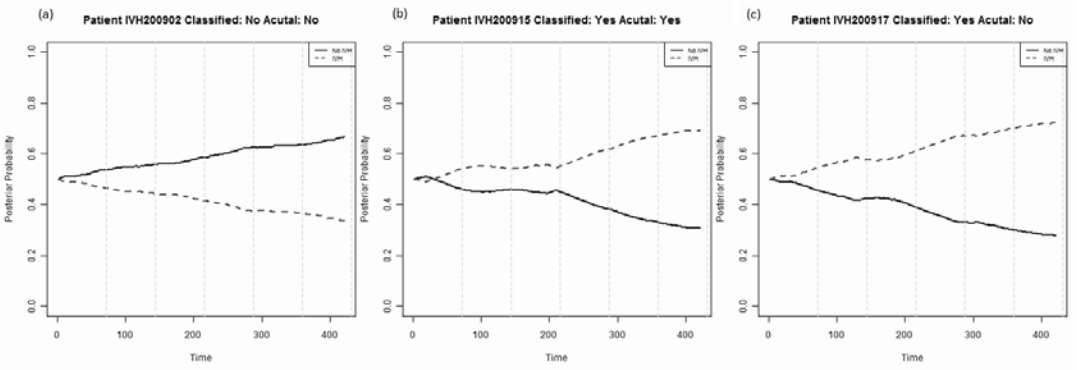

Figure 2: Posterior probability plots for (a) a subject that didn't experience IVH and was correctly classified, (b) a subject that did experience IVH and was correctly classified, and (c) a subject that didn't experience IVH and was NOT correctly classified

was evaluated using leave-one-out cross-validation. The 72 hour sensitivity and specificity were 100% (5/5) and 88.2% (15/17), respectively. Sensitivity and specificity at 5, 10, and 12 hours were all 80% (4/5) and 82.4% (14/17), respectively.

To visualize the classification process, posterior probabilities were plotted across all time points for each subject. Figure 2 gives three such plots that demonstrate the utility of this method. Plots (a) and (b) show how the posterior probabilities of two subjects that were correctly classified as "not at risk" and "at risk", respectively, began to diverge toward those correct group assignments from very early on in the study. A clinician monitoring subject (a) in real time would presumably have noticed the subjects c-TOI measures fit the profile of the "not at risk" group and given no IVH intervention. Likewise, a clinician monitoring subject (b) would presumably have noticed this subects c-TOI measures aligning with the "at risk" group and considered IVH intervention. The plot in (c) belonged to a subject that did not experience IVH during the study period but was identified as "at risk" by the proposed classification method. Further investigation revealed severe IVH was detected in this subject approximately one month after the study's conclusion when the subject was readmitted to the hospital for NEC related complications. It is interesting to note the proposed method picked up on this subjects predisposition to severe IVH even though it happened outside of the usual 72 hour window.

4. Discussion

In this paper we present a sequential naïve Bayes classifier for continuous data patterned after a similar classifier proposed in Anderson and Dubnicka (2009) for discrete data. Prior probabilities and kernel density estimates play an important role in using this classifier and considerations such as the type of kernel used as well as the bandwidth can effect the quality of the estimated conditional probability. For this paper, uniform priors, a gaussian kernel, and bandwidth selected using Silverman's rule of thumb (Silverman 1986) were used. Different bandwith estimates and kernel options such as epanechnikov, cosine, and biweight are possible. While estimates are expected to be somewhat robust to kernel choice, estimates are likely to be sensitive to the bandwidth selected. Incorporating more informative

priors to account for gestational age, or other protective demographics such as maternal antenatal steroid use remains a topic of future work. Also to be noted is the assumption of independence between consecutive observations when using the naïve Bayes classifier. Clearly the repeated measures obtained over the course of the study mentioned in this paper will be correlated. While the proposed method ignores this feature of the data, it is anticipated that incorporating the correlation structure of the data will lead to improved classification rates, making the proposed method, a lower bound of sorts on the classification rate. Zhang (2004) discusses the surprisingly good performance of naïve Bayes classifiers even when the assumption of independence is unwarranted. They point out one reason for this may be that while the true probability may not be accurately estimated, the classifier can still make the correct assignment as long as the correct group is the most probable. Incorporating the correlation of the observations remains a topic of research for this method.

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