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A probabilistic approach for lateralization of seizure onset zone in drug-resistant epilepsy with bilateral cerebral pathology

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ABSTRACT

Background: Lateralization of seizure-onset zone (SOZ) during electroencephalography (EEG) monitoring in people with bilateral potentially epileptogenic lesions is important to facilitate clinical decision making for resective surgery.

Methods: We develop two Bayesian approaches for estimating the number of consecutive ipsilateral seizures required to lateralize the SOZ to a given lower limit of 95% credible interval (LLI, assuming continuous prior distribution), or to a given posterior probability (assuming mixture of discrete and continuous prior probabilities).

Results: With estimation approach, if both the cerebral hemispheres are a priori equi-probable to contain SOZ, then using Jeffrey's prior, a minimum of 9, 18, and 38 consecutive ipsilateral seizures will yield an LLI of 0.81, 0.90, and 0.95 respectively. If one of the hemisphere is *a priori* more likely to have SOZ, then prior beta distributions with $\alpha = 3$, $\beta = 2$, and $\alpha = 4$, $\beta = 3$ will require a minimum of 18 and 24 consecutive ipsilateral seizures to yield an LLI of 0.80. Contrariwise, the testing approach allows approximation of the number of consecutive ipsilateral seizures to lateralize the SOZ depending on an estimate of prior probability of lateralized SOZ, to a desired posterior probability. For a prior probability of 0.5, using uniform prior, mixture model will require 7, 17, and 37 consecutive ipsilateral seizures to lateralize the SOZ with a posterior probability of 0.8, 0.9, and 0.95 respectively.

Conclusion: While the reasoning presented here is based on probability theory, it is hoped that it may help clinical decision making and stimulate further validation with actual clinical data.

1. Introduction

In people with epilepsy having bilateral cerebral pathology, for example from hypoxic-ischemic injury or bilateral mesial temporal sclerosis, a frequent question during video electroencephalography (EEG) monitoring relates to lateralization of seizure-onset zone (SOZ). Often, surgical decision making is crucially dependent on this information if the seizures are drug-resistant. Particularly, resective surgery can be considered only if the SOZ has a consistent lateralization. In case of bilateral independent seizure-onsets, palliative options like corpus callosotomy or vagus nerve stimulation are usually offered. During EEG monitoring, if independent bilateral seizure-onsets are detected early enough, then the decision making is relatively straight-forward. However, if seizures continue to arise from only one hemisphere, the clinician is faced with a dilemma: how many seizures arising from any one hemisphere are needed before it can be inferred with a given level of confidence that the patient probably has a lateralized SOZ? Unfortunately, this question cannot be answered based on pathophysiology, as the other hemisphere may indeed have dormant or potential epileptogenic networks which may be recruited at a later time [1,2]. However, a purely mathematical reasoning may partially help decision making in this difficult situation.

2. Methods

We present two Bayesian approaches for this problem. The first method is estimation-based and examines the lower limit of one-sided 95% credible intervals. It is essentially equivalent to assessing

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the strength of evidence for a lateralized SOZ. The second method is testing-based and examines the posterior probability that the SOZ is limited to one hemisphere of the brain. This is a decision approach as to whether the SOZ is unilateral or bilateral.

2.1. Estimation approach

We first modeled the binomial probability of x seizures from one specified hemisphere (for example: left) out of a total of n seizures. If θ is the probability that a seizure occurs in the specified hemisphere, then:

$$P(x|\theta) = \text{Binom}(x;\theta,n) = \binom{n}{x}\theta^x(1-\theta)^{n-x}$$

Here, the probability that a seizure occurs in the contralateral hemisphere (in our example: right) is $1-\theta$. We then assigned the prior distribution of the probability θ using the beta distribution:

$$p(\theta) = \text{Beta}(\theta;\alpha,\beta) = \frac{1}{\text{Beta}(\alpha,\beta)}\theta^{\alpha-1}(1-\theta)^{\beta-1}$$

where Beta(α,β) serves as a normalization constant to ensure that the total probability integrates to 1. It is important to note that the expected value of θ under the prior distribution above is $\alpha/(\alpha+\beta)$. This is the expected value of θ before any data are observed, that is the prior expectation [5]. The beta distribution is especially useful in modeling values that lie between 0 and 1, and it is also a conjugate prior for the binomial distribution [3]. In other words, the distribution of θ given that x is observed, is still a beta distribution, although with different parameters. Now, using Bayes' theorem the posterior distribution can be written as follows, omitting the normalizing marginal distribution of x alone in the denominator, which is not a function of θ:

$$f(\theta|x) \propto p(x|\theta).p(\theta) \propto \theta^{(x+\alpha)-1}(1-\theta)^{(n-x+\beta)-1}$$

Thus, the posterior distribution is itself a beta distribution:

$$p(\theta|x) = \text{Beta}(\theta;\alpha+x,\beta+n-x)$$

Note that the parameters of this function include the parameters from the prior distribution α and β, and the observed data x and $n-x$. Thus, the lower 5th percentile of this posterior distribution gives a lower limit for θ at a probability level of 0.95. We will refer to it as the lower limit of the 95% credible interval (LLI). Using the equation above for the expectation from a beta distribution, the expected value of the parameter θ given the observed value x is:

$$E(\theta|x) = \frac{\alpha+x}{(\alpha+x)+(n+\beta-x)}$$

This can be re-written as:

$$E(\theta|x) = \frac{x}{n}\left(\frac{n}{n+\alpha+\beta}\right) + \frac{\alpha}{\alpha+\beta}\left(\frac{\alpha+\beta}{n+\alpha+\beta}\right)$$

Note that the above conditional expectation is a convex combination of x/n, the empirical estimate of θ based only on the data, and $\alpha/(\alpha+\beta)$, the expected value of the proportion θ based only on the prior distribution. Since the prior distribution of θ is a continuous beta distribution, this approach can also be referred to as the continuous model.

2.2. Testing approach

Let E be the indicator random variable representing whether the SOZ is unilateral (u) or bilateral (b) with marginal probabilities (Eq. (1)):

$$P(E=u) = q \text{ and } P(E=b) = 1-q \quad (1)$$

where $0 < q < 1$ is the prior probability that the SOZ is unilateral as specified by the epileptologist based on clinical information. Using this specification, we can formulate the clinical question, i.e. whether the SOZ is "truly" unilateral, in terms of following hypotheses:

$$H_1 : E = u \; vs. \; H_2 : E = b$$

Hence, the prior probabilities of the hypotheses are:

$$P(H_1) = q, \text{ and } P(H_2) = 1-q$$

Now, let $p \in [0,1]$ be the probability of a seizure occurring from the left hemisphere (for example), which is unknown, and we assign the following prior distribution for p, conditional on E, such that:

Case I. conditional on $E=u$, p takes values of 0 or 1, and we assign equal prior probabilities (Eq. (2)):

$$P(p=1|E=u) = \frac{1}{2} = P(p=0|E=u) \quad (2)$$

Case II. conditional on $E=b$, p takes values in the range (0,1) and we assign the uniform prior distribution:

$$p|E \sim U(0,1)$$

which is also the Beta(1,1) distribution with probability density given by (Eq. (3)):

$$P(p|E=b) = 1 \text{ for } 0 < p < 1 \quad (3)$$

Eqs. (1)–(3) define the joint (prior) distribution for (E,p) which yields a mixture marginal distribution with discrete and continuous components, for p.

As in the estimation approach, we observe x, the number of seizures with left hemisphere onset, out of n seizures, and assume that it has a Binomial(n,p) distribution. Given data x, we calculate the posterior probabilities of the hypothesis H_1, $P(H_1|x)$ and the physician can use it to make a decision as to whether the SOZ is "truly" unilateral. This decision will be based on $P(H_1|x) > C$, for some pre-set threshold value C, for example $C=0.95$, and report $1-P(H_1|x)$ as the associated error probability. The posterior probability of H_1 is (Eq. (4)):

$$P(H_1|x) = \frac{P(x|H_1)P(H_1)}{P(x)} \quad (4)$$

where the denominator $P(x)$ is the unconditional probability that there are x seizures recorded with left hemisphere onset. Given that H_1 takes values 0 or 1 and using Eq. (2):

$$\begin{aligned} P(x|H_1) &= P(x|H_1, p=0)P(p=0|H_1) + P(x|H_1, p=1)P(p=1|H_1) \\ &= \frac{1}{2}P(x|H_1, p=0) + \frac{1}{2}P(x|H_1, p=1) \end{aligned}$$

and hence (Eq. (5)):

$$P(x|H_1) = \begin{cases} \frac{1}{2} \; if \; x = 0 \; or \; n \\ 0 \; if \; 0 < x < n \end{cases} \quad (5)$$

Given H_2, $p \sim U(0,1)$ and using the Binomial distribution for $x|p$ (Eq. (6)):

$$\begin{aligned} P(x|H_2) &= \int P(x|p,H_2)P(p|H_2)dp \\ &= \int_0^1 \binom{n}{x}p^x(1-p)^{(n-x)}dp = \frac{1}{n+1} \end{aligned} \quad (6)$$

The above follows from the following equation derived using the Beta distribution [4]:

$$\int_0^1 p^x(1-p)^{n-x}dp = \text{Beta}(x+1,n-x+1) = \frac{x!(n-x)!}{(n+1)!}$$