Inferring Seizure Frequency From Brief EEG Recordings

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Abstract: Routine EEGs remain a cornerstone test in caring for people with epilepsy. Although rare, a self-limited seizure (clinical or electrographic only) may be observed during such brief EEGs. The implications of observing a seizure in this situation, especially with respect to inferring the underlying seizure frequency, are unclear. The issue is complicated by the inaccuracy of patient-reported estimations of seizure frequency. The treating clinician is often left to wonder whether the single seizure indicates very frequent seizures, or if it is of lesser significance. We applied standard concepts of probabilistic inference to a simple model of seizure incidence to provide some guidance for clinicians facing this situation. Our analysis establishes upper and lower bounds on the seizure rate implied by observing a single seizure during routine EEG. Not surprisingly, with additional information regarding the expected seizure rate, these bounds can be further constrained. This framework should aid the clinician in applying a more principled approach toward decision making in the setting of a single seizure on a routine EEG.

Key Words: Bayes rule, Seizure frequency, Statistical inference, EEG.

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Most epilepsy centers rely on brief (<30 minutes) EEG recordings for diagnostic purposes. Occasionally, a patient has a seizure during the study. Such an event might suggest a high underlying seizure rate because otherwise the chance of observing a seizure during any brief interval is low. Alternatively, one might argue that a single seizure may have simply been a rare event in a patient with a low underlying seizure rate and that occasional seizures are expected in a high-volume EEG service by chance alone. An accurate estimation of the underlying seizure frequency has important clinical implications, dictating whether to pursue further testing, recommend medication changes, or continue a watchful waiting approach. We explore these opposing perspectives within a principled probabilistic framework and show that each may be appropriate under different circumstances. We offer concrete suggestions for how to make appropriate clinical decisions across a range of circumstances in which a single seizure is observed on routine EEG.

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METHODS

Mathematical Model for Seizure Event Times and Rates

We assume seizures occur at random times, following a Poisson process (Bishop, 2006) with an unknown rate (r) between 0 and some maximal physiologically plausible rate R_{max}. Thus, the probability that a given number of seizures (κ) occur in a time interval of length T is

$$P(\kappa/r, T) = (rT)^{\kappa} e^{-rT}/\kappa.$$

In the following sections, we assume that we have observed 1 seizure ($\kappa = 1$) during a "routine" outpatient EEG recording lasting $T = 30$ minutes.

We explore the effects of different possible pre-EEG estimates of seizure rate by examining how different assumptions regarding pretest probability estimates of seizure frequency, denoted $P(r)$, affect posttest estimates of seizure rate, denoted $P(r/\kappa, T)$. The relationship between the pretest probability [$P(r)$], posttest probability [$P(r/\kappa, T)$], and likelihood function [$P(\kappa/r, T)$] is specified by Bayes rule

$$P(r/\kappa, T) = (P(r)P(\kappa/r, T)/Z),$$

where Z is the normalization constant of the distribution. We model prior probability distributions over seizure rates using gamma distributions (Bishop, 2006; El-Sayyad and Freeman, 1973):

$$P(r) = \beta^{\alpha} r^{\alpha-1} e^{-\beta r}/\Gamma(\alpha),$$

where Γ is the normalization constant. The mode and standard deviation of the gamma distribution are given as follows: mode $= (\alpha - 1)/\beta$ and standard deviation $= (\sqrt{\alpha}/\beta)$. The gamma distribution is flexible enough to model a wide range of clinically relevant scenarios and has the mathematical advantage that when paired with the Poisson model for seizure event times, the posttest probability distribution [$P(r/\kappa, T)$] is also a gamma distribution (Bishop, 2006). Updated values for the posttest distribution are given by simple formulas (Bishop 2006; El-Sayyad and Freeman, 1973), namely, α is updated to $\alpha + \kappa$, and β is updated to $\beta + T$. Specific values of α and β used in the figures, together with the corresponding mean and variance values from which they are computed, are as follows, with values given in the format (mean, standard deviation, α, β): for Figure 1A, the values are (4,1, 17.9, 4.2) and (4.2, 1.0, 18.9, 4.2), and for Figure 1B, they are (4, 8, 1.6, 0.2) and (10.2, 10.1, 2.6, 0.2). As explained below, Figure 2 was constructed assuming a uniform distribution over the range from 0 to 4,3200 seizures per month, coupled with the following values for the likelihood function: $\kappa = 1$ and $T = 30$ minutes.

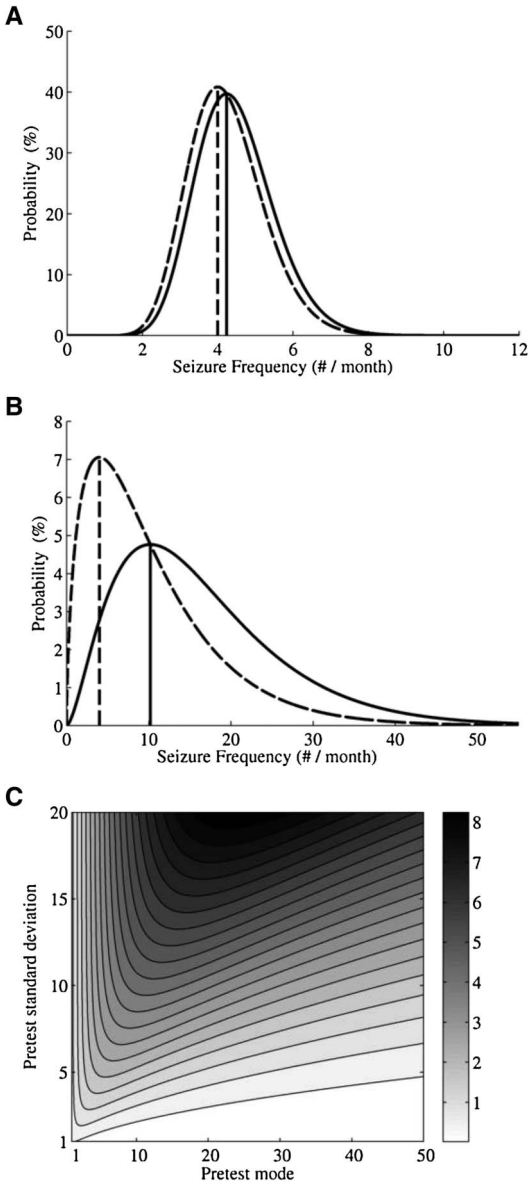

FIG. 1. A, Pre- and posttest probability distributions for seizure frequency, assuming a tight (narrow) pretest probability distribution. Dashed line: pretest probability distribution, mode = 4.0, standard deviation (SD) =1; solid line: posttest probability distribution, after observing a single seizure during a routine 30-minute EEG recording, mode 4.24, SD = 1.03. The mode of each distribution is indicated by a vertical line. B, Same as the previous one (A), now assuming loose (broad) pretest probability distribution. Dashed line: pretest probability distribution, mode = 4, standard deviation =8; solid line: posttest probability distribution, after observing a single seizure during a routine 30-minute EEG recording, mode 10.2, standard deviation = 10.06. C, Contour plot illustrating the relationship between uncertainty in the pretest probability estimate ("pretest standard deviation") and the change in the best estimate of the patient's seizure frequency (mode of the posterior distribution) after observing a single seizure on a 30-minute EEG; the amount of change is encoded in the gray scale. Values are in units of seizures per month.

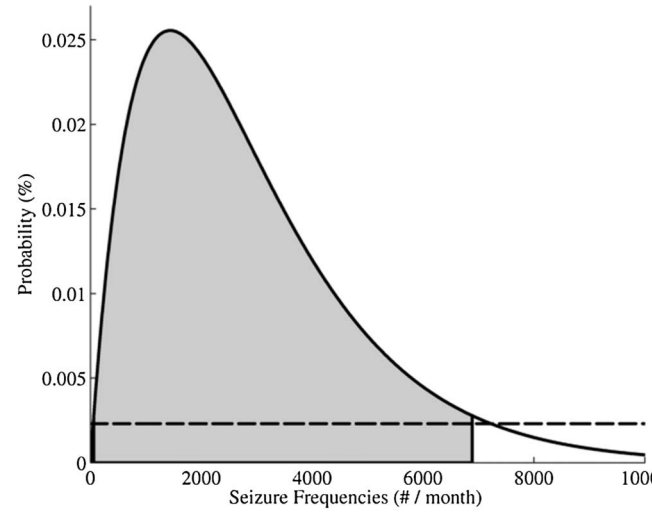

FIG. 2. Pre- and posttest probability distributions for seizure frequency, assuming a uniform pretest probability distribution, with maximum possible rate assumed to be 43,200 per month (1 seizure/minute). Dashed line: pretest probability (uniform distribution); solid line: posttest probability distribution, after observing a single seizure during a routine 30-minute EEG recording. The portion of the distribution containing 95% of the total probability mass is shaded.

RESULTS

Scenario 1: Unbiased Ignorance

First consider the situation where the EEG reader knows no clinical details of the case and wishes to "let the data speak for itself." More explicitly, assume that there is no a priori reason to favor any particular value in the large range of possible seizure rates (0 through R_{max}); hence, before seeing the EEG, the prior probability distribution is uniform across this range. In this case, Bayes rule dictates that the shape of the posttest probability distribution is governed entirely by the shape of the likelihood function. We specify the range of "plausible" seizure rates as those for which there is a 95% probability that the true seizure rate lies between them.

This distribution is shown in Figure 2, along with the boundary of the range containing 95% of the probability. We assume a theoretical maximum possible rate of 1 seizure/minute (approximately 43,200 per month). The 95% probability interval in this case of an uninformed prior probability distribution is broad, approximately 120 to 13,778 seizures per month (4–459 seizures/day). As intuition would suggest, the most probable seizure rate (the mode of the distribution) is simply 1 seizure per half hour, or 1,440 seizures per month. Lower rates are of course possible but less probable. For example, the probability that the true rate is <4 per month would be judged $<0.001\%$.

Scenario 2: Well-Known Seizure Frequency

Next, suppose instead that we have reliable clinical and/or prior EEG information suggesting that the most likely baseline seizure frequency is 4 per month and that we are fairly confident of this estimate (e.g., suppose the error is not much more than ± 1 seizure per month). For example, this level of confidence could be afforded by a meticulous seizure diary kept by a reliable reporter, such as a patient whose seizures do not impair awareness or an

observant family member who spends sufficient time with the patient. The resulting probability distribution, depicted by the dashed curve in Figure 1A, serves as the pretest probability distribution regarding seizure frequency.

We now update this distribution, incorporating the observation of a single seizure in a 30-minute recording, again using Bayes rule. The solid curve in Figure 1A shows that in this case, the posttest probability distribution is not much changed from the pretest distribution: The mode increases by a clinically insignificant amount from 4 to 4.24 seizures per month. Because the seizure frequency is fairly certain before testing, the single observed seizure has little impact on our clinical impression of seizure frequency. Bayes rule helps us reconcile that while the observation is surprising (the probability that a single seizure occurs during any given 30-minute EEG recording is only 0.27%–0.29%), this observation is counterbalanced by our strong prior knowledge that the seizure frequency was low.

Scenario 3: Poorly Known Seizure Frequency

Suppose now that information about the patient's seizure rate is less certain, as when the history is unreliable, we have only known the patient for a brief time, or we suspect the patient is often unaware of seizures (Blum et al., 1996; Burneo, 2008; Hoppe et al., 2007; Kerling et al., 2006). Here, we expect a single observed seizure to carry relatively more weight because the prior knowledge is weak. Suppose our pretest probability distribution has a mode of 4 seizures per month and a large standard deviation of, say, 8 seizures per month. This level of (un)certainty might be arrived at, for example, in managing a patient who is not able to reliably report an accurate seizure frequency but for whom we have arrived at a baseline estimate based on short-term monitoring data collected via ambulatory EEG or admission to an epilepsy monitoring unit. In such a case, a single seizure in a 30-minute test causes us to increase our estimate of the most likely seizure frequency by approximately 6, from 4 up to 10.1 seizures per month (Fig. 1B).

Adjusting Frequency Estimates After a Seizure on Routine EEG: A Clinical Guide

As suggested by our three examples, the degree of uncertainty in our pretest estimates of seizure frequency determines the amount by which our estimates are influenced by observing a seizure during a brief EEG recording; uncertain pretest estimates should always be more heavily influenced by new data. Figure 1C illustrates this general relationship and may serve as a clinical guide to adjusting one's pretest probability estimate of seizure frequency after seeing a seizure on a brief EEG recording. For example, a pretest estimate of 2 ± 2 seizures per month (mode $\pm$ standard deviation) is adjusted upward to 3.2 ± 2.3, an increase of 1.2, whereas a less certain pretest estimate of 2 ± 4 is affected more, increasing to 5.1 ± 5.1. Similarly, a pretest rate of 20 ± 20 is increased by 12.1, to 32 ± 23.3, whereas a less certain a priori estimate of 20 ± 40 increases by more than double to 50 ± 49.7.

"Don't Be Fooled by Randomness": The Fallacy of Division

Finally, consider the following line of reasoning, the "don't be fooled by randomness"(Taleb, 2001) argument: In any large number of routine EEGs, we are bound to see a few seizures "by chance," even if all patients' underlying seizure rates are low. For example, if we perform a routine (30 minutes) EEG on 5,000 patients who all have seizures at average rates of 1 per month, then we should expect to see 3 to 4 seizures among this set of recordings. Thus, a single seizure during a routine EEG recording need not imply a high underlying seizure rate.

While this observation correctly points out that a single seizure does not *necessarily* imply a high underlying seizure rate, it is problematic to conclude that the underlying rate is *probably* actually low in any given individual. While inference is straightforward when specific information about an individual's seizure rate is known (Scenario 2), the most appropriate choice of prior probability distribution when no specific clinical information exists is not obvious. When the population referral base is broad and inhomogeneous, as is often the case, the true underlying distribution of rates for the population may have multiple peaks or "fat tails" (nonnegligible probability at high rates); such "fat-tailed" distributions are notoriously difficult to accurately measure empirically and are susceptible to severe underestimation, especially with respect to low probability events (Taleb, 2001; Taleb, 2010). Thus, the "don't be fooled by randomness" approach leaves one vulnerable to discounting outliers who actually do have very high seizure rates as a result of model inaccuracies.

By contrast, the "unbiased" approach of modeling all possible seizure rates as a priori equally probable leads to the conclusion that the underlying seizure rate is likely to be high, although the range of probable rates will be quite broad (see Scenario 1). The primary consequence of this approach is to lead one to seek further clinical information, which can either confirm a high seizure rate and lead to appropriate medical intervention or provide reassurance that the observed seizure was most likely a rare event on a background of infrequent seizures.

The above discussion suggests that the impulse to discount the significance of a seizure during routine EEG based on "don't be fooled by randomness" reasoning is generally a variation on the "fallacy of division" making inferences about individuals by assuming that individual members of a group have the typical characteristics of the group (Robinson, 2009).

DISCUSSION

We have seen that a single seizure during a brief routine EEG recording can have very different implications depending on the prior clinical information available. In cases where nothing is known beyond the EEG, a conservative assumption that all physiologically plausible seizure rates are equally likely necessarily lead us to suspect that the underlying seizure rate is quite high. Alternatively, when prior clinical data constrain the true underlying seizure frequency within a narrow range, a single seizure is properly interpreted as a rare event, and estimates of the underlying seizure rate remain heavily determined by the prior clinical knowledge. In intermediate cases, with less certain clinical data, the posttest probability distribution is determined by substantial contributions from both prior information and the EEG data. Finally, we have argued the need for caution in discounting a single seizure in an individual on the grounds that occasional seizures are expected by chance alone in a large set of EEGs because this reasoning falls prey to fallacy of division.

These considerations lead us to offer the following concrete, situation-dependent recommendations, summarizing appropriate reactions and reasoning in response to a single seizure during a routine recording. The recommendations apply to patients of all ages, and in the final analysis, they may seem commonsensical.

However, these issues have arisen repeatedly over many years in discussions among the authors and colleagues; therefore, we believe that it is useful to state these recommendations explicitly.

Scenario 1: No Prior Knowledge

A single seizure implies a high underlying rate of seizures (hundreds to thousands per month), until proven otherwise. More information should be sought until the true seizure frequency can be estimated with sufficient confidence to allow appropriate clinical action, for example, by speaking with the patient, family members, caretakers, or referring physician; reviewing prior EEG data; or obtaining a follow-up or longer EEG recording.

Scenario 2: Tightly Known Seizure Frequency

If prior information supports a fairly low seizure probability with reasonable certainty, then the single event need not lead to any substantive revisions of clinical impression or alter previous management decisions. Nevertheless, the sensitive dependence of this conclusion on the prior probability distribution serves as a cautionary reminder to be careful how confident we are about our prior estimates, especially in cases where seizures are likely to be underreported (e.g., seizures which the patient is unaware of are likely to be underreported if they produce subtle manifestations or if the patient lives alone).

Scenario 3: Loosely Known Seizure Frequency

This case is intermediate between scenario 1 and scenario 2 and simply requires an intermediate level of intensity of further investigation.

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