Received: 7 May 2019 | Accepted: 7 May 2019

DOI: 10.1002/epi4.12328

COMMENTARY

Epilepsia Open® Open Access

Does my posterior look big in this?—Bayesian solutions to seizure counting problems

Blake Cook[1] | **Mark Cook**[2]

[1]EPSRC Centre for Predictive Modelling in Healthcare & Living Systems Institute, University of Exeter, Exeter, UK

[2]Graeme Clark Institute, University of Melbourne, Victoria, Australia

Correspondence
Mark Cook, Graeme Clark Institute, University of Melbourne, Vic. 3052, Australia.
Emails: markcook@unimelb.edu.au

All models are wrong, but some are useful.
—(George E. P. Box)

Uncertainty regarding true seizure frequency remains a major obstacle to the management of seizures. There are two separate but related problems—the apparent unpredictability of events and the difficulty accurately capturing events using patient reporting with diary-based systems. All clinicians are familiar with the experience of increasing medication doses, sometimes repeatedly, in response to reported fluctuations in seizure frequency that may simply represent the underlying variability of the condition, or variations in the accuracy of reporting.

More recently, work with implantable seizure monitoring systems[1,2] has allowed better recognition of underlying patterns of seizure activity, permitting the generation of more sophisticated modeling of changes in seizure occurrence, rather than simple frequency counts. Evidence of long-term memory,[3] patterns to interseizure interval patterns,[4] and strong circadian and ultradian rhythms[5] has led to the development of useful forecasting techniques.

The disparities between true seizure frequency and diary-based patient-recorded events are well recognized.[6,7] Studies examining EEG monitoring unit data,[8] ambulatory EEG,[9] and implanted or wearable systems have consistently shown that seizures are frequently unrecognized and unreported. The type of seizure and "diary fatigue" are important elements also. Some seizure types are particularly prone to underreporting, particularly focal impaired awareness events and those which occur in sleep. A variety of novel solutions have been developed to improve on this with the increasing sophistication and sensitivity of wearable devices.[10] Strategies to accommodate this information in clinical practice and drug trials would be of great utility.

Bayes' theorem describes the probability of an event while accommodating prior knowledge of conditions related to the event. This provides a method of updating our perceived probabilities of events according to available evidence—Bayesian inference. With this, the degree of probability will rationally alter in accordance with the availability of relevant evidence. The technique of Bayesian inference is fundamental to Bayesian statistics, and the methods are particularly valuable for dealing with incomplete data.

When data are incomplete, it is necessary to make some—necessarily subjective—assumptions about the underlying parameters of the statistical model. The Bayesian approach does not assume a fixed underlying parameter, but instead allows for uncertainty in the parameter space and provides inferences on the most likely model parameters, given what the data show. Incomplete data are well-suited to the Bayesian approach as it allows the subjective component of inference to be formalized. These techniques are of widespread use in many machine-learning fields particularly and are increasingly being applied in medicine.

Hidden Markov models (HMMs) are sometimes described as the simplest dynamic Bayesian system, and unlike a standard Markov model where the current state is observed, in the hidden Markov model the state is not directly observable, but some output of the state is measurable. These models provide a framework to determine the probability of hidden states based on observed output. These techniques are good for modeling temporal data series, and Markov models and hidden Markov models are well-suited to model flat stretches and bursts in time-series data, and so are appropriate to the clinical situation of often long seizure-free intervals, punctuated by bursts or clusters of activity. They can be used to estimate the amount of time a patient will stay in a low seizure risk state for instance.

These more sophisticated approaches, combined with the knowledge of underlying patterns of seizure activity, together with large databases of electronic seizure diaries, afford a unique opportunity to develop better methods of interpreting reported seizure counts. These models can accommodate a great deal of complexity, and incorporate other clinical measures as they become available, such as data from wearables.

Chiang and colleagues have taken a novel approach to tackling these problems and propose a Bayesian method of analysis, which can be applied to individual seizure records, which then assesses changes in seizure risk rather than observed seizure counts, and so avoids the effects of natural fluctuations in frequency. They model seizure occurrences as a point process where the frequency of seizures is a hidden parameter that follows a discrete Markov process, and they use Bayesian techniques in order to update the underlying hidden transition probabilities based on observed data. As well, they use the concept of a measure of "seizure control" rather than simply reported seizure events. This solution also allows for missed data to be incorporated in the estimations, based on recognition of the reproducible patterns underlying seizure activity. They demonstrate this approach is superior to the standard method of seizure counts to estimate seizure risk. This allows more appropriate responses to managing seizures clinically and importantly could potentially be extended to a better way of interpreting clinical trial data. Data obtained from a large and unique database, SeizureTracker, have been used for the study, and while a particular clinical group has been studied (tuberous sclerosis), the method is of broad applicability.

The authors have introduced a powerful technique, which may allow us to approach management in a more personalized manner, and improve patient outcomes, and reduce overtreatment. The work represents an important step forward in our approach to the analysis of data in the management of epilepsy.

Read the winning article: "Epilepsy as a dynamic disease: A Bayesian model for differentiating seizure risk from natur al variability"

CONFLICT OF INTEREST

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Cook MJ, O'Brien TJ, Berkovic SF, Murphy M, Morokoff A, Fabinyi G, et al. Prediction of seizure likelihood with a long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. Lancet Neurol. 2013;12:563–71.
2. Baud MO, Kleen JK, Mirro EA, Andrechak JC, King-Stephens D, Chang EF, et al. Multi-day rhythms modulate seizure risk in epilepsy. Nat Commun. 2018;9(1):88.
3. Cook MJ, Varsavsky A, Himes D, Leyde K, Berkovic SF, O'Brien T, et al. The dynamics of the epileptic brain reveal long-memory processes. Front Neurol. 2014;24(5):217.
4. Karoly PJ, Freestone DR, Boston R, Grayden DB, Himes D, Leyde K, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. Brain. 2016;139:1066–78.
5. Karoly PJ, Goldenholz DM, Freestone DR, Moss RE, Grayden DB, Theodore WH, et al. Circadian and circaseptan rhythms in human epilepsy: a retrospective cohort study. Lancet Neurol. 2018;17:977–85.
6. Fisher RS, Blum DE, DiVentura B, Vannest J, Hixson JD, Moss R, et al. Seizure diaries for clinical research and practice: limitations and future prospects. Epilepsy Behav. 2012;24:304–10.
7. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. Arch Neurol. 2007;1(64):1595–9.
8. Blum DE, Eskola J, Bortz JJ, Fisher RS. Patient awareness of seizures. Neurology. 1996;47:260–4.
9. Tatum WO, Winters L, Gieron M, Passaro EA, Benbadis S, Ferreira J, et al. Outpatient seizure identification: results of 502 patients using computer-assisted ambulatory EEG. J Clin Neurophysiol. 2001;18:14–9.
10. Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. Lancet Neurol. 2018;17:279–88.