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Dealing with Zero-Numerators in Estimating Drug-Dependence Chances: A Bayesian Approach

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Dealing with zero-numerators in estimating drug-dependence chances: A Bayesian approach.

Abstract

Aims: At CPDD 2015, we applied parametric Hill functions to estimate the probability of drug dependence in relation to the duration of drug-taking experience. A problem we and others have encountered in the estimation of risk of becoming a drug-dependence case is an observed point estimate of zero – the so-called “zero-numerator problem.” This problem can be easily observed in certain low risk subgroups even when the sample is large (e.g., the incidence of heroin dependence among 12 year-old newly incident heroin users) or with small subgroup sample sizes. In these instances, tan observed zero point estimate does not necessarily imply zero risk of developing dependence for the subgroup. Here, our aim is to describe our approach to a potential solution to the zero-numerator problem based on a Bayesian model in conjunction with parametric Hill functions.

Methods: The traditional frequentist statistical approach can provide an estimate for the 95% upper bound of an incident rate even with the observed zero in the numerator. A Bayesian approach is required if estimation of the incident rate itself is of interest. The Bayesian approach demands specification of a prior distribution for the risk parameter. In this work, we are exploring the sensitivity of the Hill function parameter estimates to the choice of a particular informative prior distribution across a range of estimated chances of developing drug dependence very soon after onset of drug use.

Conclusions Whereas we frame our work in relation to risj of developing drug dependence syndromes, the zero-numerator problem often is faced in other contexts (e.g., pharmacokinetics, toxicology). Our approach, combining Bayesian statistics in conjunction with Hill functions, is expected to provied a useful solution to these zero numerator problems.

The Zero-Numerator Problem

# Smoking days past month	n (unweighted)	y (# Dependent)	$\hat{p}$ (weighted)
1	490	4	0.01
2	233	8	0.03
3	137	2	0.01
4	91	2	0.02
5	78	1	0.01
6	25	0	0.00
7	39	1	0.02
8	27	2	0.07
9	15	0	0.00
10	70	4	0.04
11	1	0	0.00
12	19	1	0.00
13	10	0	0.00
14	7	0	0.00
15	64	2	0.03
16	4	0	0.00
17	1	0	0.00
18	5	0	0.00
19	1	0	0.00
20	47	4	0.06
21	4	1	0.56
22	7	0	0.00
23	2	1	0.61
24	5	0	0.00
25	22	1	0.08
26	3	1	0.37
27	4	0	0.00
28	7	3	0.65
29	9	4	0.31
30	88	24	0.23

Table 1: Unweighted numbers of rapid incident onset (within 3 months of use) smokers with the corresponding weighted probability of nicotine dependence.

Consider data from United States (US) National Surveys on Drug Use and Health (NSDUH) 2004 – 2013, over $n = 1,515$ (unweighted) subjects with smoking onset within 3-months of assessment, who had smoked at least once during the past 30 days.

Suppose we want to estimate the probability of nicotine dependence, p , given 6 days of smoking past month. Out of 25 subjects, none was qualified as a nicotine dependence case. Having observed no occurrences of the event does not imply that it has a zero probability of occurrence. This situation is referred to as the zero-numerator problem and it's instances are highlighted in gray in Table 1.

The zero-numerator problem can be approached with a Bayesian model. It is well known that a $Beta(a, b)$ is a conjugate prior for the binomial distribution $Bin(n, p)$ and the corresponding posterior is $Beta(y + a, n + b - y)$.

Different Choices for Informative Priors

Often researchers want the data ‘to dominate’ and thus assign a prior probability of an event that is ‘uninformative’ or vague in some sense. However, if one puts vague prior distributions on the parameter values, e.g., $p \sim Beta(1, 1)$ (uniform prior) then, in practice, all values of nicotine dependence probability are equally likely after X smoking days past month – an unlikely scenario in the zero-numerator setting. Additionally, with a correctly specified informative prior, Bayesian inference is not susceptible to selection bias, e.g., how many smoking days past month is associated with the highest risk of nicotine dependence? or to multiple comparisons. Next, we will look at the role of different informative priors on the results in zero-numerator problems.

We propose $Beta(a, b)$ priors with a and b chosen to reflect prior knowledge about p – the probability of dependence after X smoking days. To capture this knowledge, we consider a ‘rolling window’ across $X - w$ and $X + w$ days. The parameters a and b are obtained as follows:

- Assume a uniform $Beta(1, 1)$ distribution of dependence probability over the $X \pm w$ smoking days window.
- The likelihood is formed as a product of the binomial densities over $X - w, \dots, X - 1, X + 1, \dots, X + w$ smoking days. Note, the information at X smoking days is excluded from the likelihood formation.
- The posterior probability of dependence over the $X \pm w$ smoking days follows $Beta(a, b)$ distribution with:
$$a = (\text{\# of dependent cases after } X - w, \dots, X - 1, X + 1, \dots, X + w \text{ smoking days}) + 1$$
$$b = (\text{\# of subjects without dependence over the same window}) + 1$$
- Under the assumption of common p – the probability of dependence over the $X \pm w$ window, – the posterior $Beta(a, b)$ becomes prior probability of dependence after X smoking days past month.

Using the above algorithm, the posterior expectations of nicotine dependence for different w ’s are illustrated in Figure 1. Since the posterior expectation is a weighted average between the prior and the posterior means, the width of the ‘rolling window’ affects the results. If the window contributing to the prior knowledge of nicotine dependence is too wide ($w = 30$), the posterior expectation is dominated by the prior overall mean (flat line in the left plot of Figure 1). If the window is narrow, e.g., $w = 1$ or $w = 2$, the posterior probabilities are sensitive to day-to-day variability in the empirical chances of dependence.

Regardless of the choice of w , the zero numerator problem is completely eliminated. So which value of w should one use in practice? **The answer can be obtained via leave-one-out cross-validation**, which in our case finds $w = 2$ to be the optimal value. The right plot of Figure 1 illustrates the posterior expectations of dependence (with the corresponding 95% credible intervals) and the weighted empirical estimates from NSDUH. Note the overlap in the 95% credible intervals and 95% confidence intervals.

Figure 1: **Left plot:** Posterior expectations of nicotine dependence for the different choices w . **Right plot:** Posterior expectation of nicotine dependence ($w = 2$) and empirical weighted probabilities from NSDUH, 2003–2014.

Hill Function Parameters

The data driven leave-one-out cross-validation algorithm can be used for selection of w – the optimal width of the ‘rolling window.’ Nonetheless, we explored the sensitivity of the Hill function parameter estimates to the choice of a particular w . The results are summarized in Table 2.

Hill Function Parameters (95% Bootstrap CI)				
w	P_{min}	P_{max}	k	PD_{50}
1	0.021 (0.016, 0.025)	0.861 (0.242, 1.000)	4.092 (2.950, 8.666)	35 (22, 45)
2	0.021 (0.017, 0.024)	0.903 (0.283, 1.000)	4.600 (3.470, 7.972)	35 (23, 41)
3	0.020 (0.017, 0.023)	0.852 (0.305, 1.000)	4.463 (3.518, 6.600)	36 (24, 41)

Table 2: Hill function parameter estimates with the 95% bootstrap confidence intervals (CI).

Based on the results in Table 2, it is evident that the Hill function parameters are robust to the particular choice of w as long as it is not ‘too distant’ from the optimal value, i.e., the width of the sliding window is not too wide. The interpretation of the Hill function parameters is as follows:

- P_{min} indicates that among newly incident smokers with only 1-3 smoking days past month, an estimated 2% had become rapid onset tobacco cigarette dependence cases.
- P_{max} shows that among newly incident smokers who smoked daily, an estimated 90% had become rapid onset tobacco cigarette dependence cases.
- PD_{50} suggests that after about 35×2 days of consecutive daily smoking, all smokers who may become dependent will most likely become tobacco cigarette dependence cases.
- k indicates the rate of transition to dependence at PD_{50} days.

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Disclosure

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