Extracting Structure from Contaminated Symbolic Data

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ABSTRACT

Symbolic data is the epitome of modern biological datasets. Modern sequencing technologies produce millions of reads giving insights on genome sequence, transcription levels, epigenetic modifications, and much more. To analyze those sequences one usually makes assumptions on their underlying structure, e.g., that the number of reads has Poisson distribution, or that transcription factor binding events occur independently at nonoverlapping promoters. These types of assumptions are often not exactly correct in reality. In fact, even when they are valid, a small amount of data “contamination” may make them appear untrue. The traditional approach to questioning assumptions on data has been hypothesis testing. This approach has various shortcomings, however. Particularly, its Boolean nature does not give room for a null hypothesis to be “approximately true.” This tutorial introduces a methodology to assess statistical assumptions on symbolic data that may be contaminated. It will give a general overview on how to approach these problems numerically, and present analytical results for some special classes of structured probability distributions. It will demonstrate the applicability of this rather new methodology with DNA methylation data to question the common but unconscious assumption that methylation of CpGs is exchangeable, and transcription factor binding site k -mers to question the use of logplots in summarizing TFBS behaviour. Data and code for this tutorial, in the form an iPython Notebook, will be made available via GitHub. This work is in collaboration with M. E. Lladser.

KEYWORDS

symbolic data, contamination, exchangeability, epigenetics, DNA methylation, independence, transcription factor binding sites

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1 SUMMARY

Models describing contamination of continuous data have been well-studied and date back to the 19th century [3]. Such models

typically assume that there is a true underlying probabilistic process producing data, and that with some small probability ϵ a sample is drawn from an alternate, or contaminating distribution. Then the probabilistic source producing observation can be described as a mixture model [1]:

$$P = (1 - \epsilon) \cdot P_0 + \epsilon \cdot R,$$

where P_0 represents the underlying process. In continuous settings, certain restrictions on the component R (such as following a Gaussian law with mean identical to P_0) are required for inference and estimation [4].

In symbolic settings, such as when data are sequencing reads, restrictions on the structure of the contamination have meaningful implications on our beliefs about the probabilistic source. Instead, we use the intuitive mixture representations above and find the smallest $\epsilon \geq 0$, with R an arbitrary probabilistic model, so that P_0 has certain desired structure. Unlike a p -value, which is highly dependent on sample size, this quantity depends only on the underlying source P and describes the fraction of data that can be expected to follow the desired structure. We present numerical methodology for approximating the amount of contamination and derive explicit expressions for this quantity in some special cases.

We demonstrate applicability of the methodology above by identifying loci where the assumption that DNA methylation is exchangeable is violated. We also identify transcription factor binding sites whose sequences are particularly poorly-described by a logoplot, because the assumption that DNA bases are independent is badly violated [2].

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