Methodological Scoping Review of Bayesian Belief Network Applications to Antimicrobial Resistance and Antibiotic Use

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1   EXTENDED ABSTRACT

Antimicrobial resistance (AMR) is an evolutionary process where microorganisms acquire ability to survive exposure to antimicrobial treatments [Vedadhir et al., 2020]. Resistance is shared across generations and between species and can occur in humans, animals, and the environment at multiple scales (individual, hospital, community, etc.), and temporalities [Vikesland et al., 2019, Phillips et al., 2004, Wooldridge, 2012, Singer et al., 2006]. Further, these interdependencies are not merely biologically complex but intertwined with social factors, making AMR a biosocially complex phenomenon [Collignon and Beggs, 2019, Tompson and Chandler, 2021].

Bayesian belief networks (BBNs) can be used for variable inference (identifying the value of variables), parameter inference (identifying probabilistic dependencies between variables) and structure learning (understanding connections among variables). BBNs are popular in many fields including ecology [Smid et al., 2010]. However, although the complexity of AMR lends itself to BBNs, their adoption in the literature has been limited. We performed a scoping review to investigate the extent, range, and nature of applications of BBNs to AMR to identify gaps and promising areas for future research.

We considered the applications of BBNs to both antimicrobial resistance and 'antibiotic use' (recognised as a major driver of resistance in bacteria [WHO, 2020]). We used a Methodological Iterative Search Technique as described by Martin et al. [2020]. Papers were identified using Boolean searches from Google Scholar, PubMed and arXiv. Additional papers were identified through a combination of pearl growing (wherein terms and keywords are identified from within papers and used to inform further searches) and citation tracking (wherein all articles cited by relevant papers are reviewed for pertinent literature, also called snowballing) [Zwakman et al., 2018, Martin et al., 2020].

In line with Martin et al. [2020], we developed five ques-tions: **1.** What problems related to AMR or 'antibiotic use' have BBNs been used to investigate? **2.** How are BBNs used (variable inference, parameter inference, structure learning)? **3.** What informs (a) the structures and (b) parameters of BBNs? **4.** How was performance of the BBNs measured? **5.** What software is used and is it freely available?

We identified 16 papers demonstrating an application of a BBN to AMR or 'antibiotic use'. Only 15 were retrievable. Five (including the inaccessible one) were related to a single BNN application, called TREAT [Kristensen et al., 2001, Paul et al., 2006a,b, Zalounina et al., 2007, 2008]. Thus, these 16 papers translated to 12 unique BBNs for analysis.

BBNs were developed either to investigate variable associations (n=5), to inform a decision tool (n=6) or both (n=1). If a paper developed a tool, it typically used a combination of variable and parameter inference. If a paper investigated associations, it generally applied structure-learning. There were two exceptions to this tradition, Sethi et al. [2018], which performed all three tasks, and Ge et al. [2014], which investigated associations of latent variables via parameter inference. When models were constructed rather than learnt they involved either experts, a literature analysis, a theory, or a combination of these factors. When structure was learnt, use of Additive Bayesian Network (ABNs) was dominant (4/5). The only other method was discrete Bayesian networks [Sethi et al., 2018]. When parameterisation was performed, there was heterogeneity in approach (expert knowledge, literature, factor analysis, data-learnt etc.). Not all papers included an evaluation of the model. Constructed-tool-based models were often evaluated in reference to other models and experts' predictions. One paper went as far as conducting cluster randomised trials on their BBNs [Paul et al., 2006b]. An AUC approach was taken up by two newer applications [Paul et al., 2006a, Wu et al., 2020] which may suggest a way forward for future evaluations. However, there is no unifying approach to comparing these tool-based models. In contrast to constructed models, the structure-learnt models exhibit homogeneity in evaluation as they typically involved bootstrap sampling and credible

intervals to develop a robust model. Structure-learnt models were typically developed using the open-source R based packages. Constructed models used more varied software, and a non-trivial amount were proprietary (n=5).

Our results suggest the limited uptake of BBNs could be partly due to complex methodologies, heterogeneity in performance measures and limitations in accessing software. Other factors may be at play, such as dominance of frequentist statistics in medical and social science fields. However, this means that for interdisciplinary teams which can navigate this landscape there are still many areas in the application of BBNs to AMR and 'antibiotic use' to be explored.

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