Environmental Modelling & Software 88 (2017) 74–83

Contents lists available at ScienceDirect

Environmental Modelling & Software

journal homepage: www.elsevier.com/locate/envsoft

Development of a microbial dose response visualization and modelling application for QMRA modelers and educators

Mark H. Weir [a, b, e, *], Jade Mitchell [c, **], William Flynn [d], Joanna M. Pope [e]

[a] Division of Environmental Health Sciences, College of Public Health, The Ohio State University, 426 Cunz Hall, 1841, Neil Ave, Columbus, OH, 43210, USA
[b] Department of Civil Environmental and Geodetic Engineering, College of Engineering, The Ohio State University, 2070 Neil Ave., Columbus, OH, 43210, USA
[c] Department of Biosystems and Agricultural Engineering, College of Engineering, Michigan State University, 524 S. Shaw Lane, East Lansing, MI, 48824, USA
[d] College of Health Sciences, 540 College Avenue, STAR Health Sciences Complex, University of Delaware, Newark, DE, 19713, USA
[e] CAMRA Consultants LLC, USA

ARTICLE INFO

Article history:
Received 15 April 2016
Received in revised form
9 November 2016
Accepted 9 November 2016

Keywords:
QMRA
Microbial dose response
Optimization
Software
Wiki

ABSTRACT

Microbial dose response modelling is vital to a well-characterized microbial risk estimate. Dose response modelling is an inherently multidisciplinary field, which collates knowledge and data from disparate scientific fields. This multidisciplinary nature presents a key challenge to the expansion of microbial dose response modelling into new groups of researchers and modelers. This research employs a dose response optimization **R** code used in 18 peer-reviewed research studies to develop a multi-functional dose response software. The underlying **R** code performs an optimization of the two primary dose response models using the MLE method and outputs statistical analyses of the fits and bootstrapped uncertainty information for the models. VizDR (Visual Dose Response) was developed to provide microbial dose response modelling capabilities to a larger audience. VizDR is programmed in JavaScript with underlying Python scripts for intercommunication with Rserve. VizDR allows for dose response model visualization and optimization of a user's own experimental data.

1. Introduction

Quantitative Microbial Risk Assessment (QMRA) modelling is a well-established tool for water quality and food safety (WHO, 2004; Haas et al., 2014; WHO, 2014). Stressors such as global climate change, global population growth, water stress and food scarcity have increased QMRA's importance for mitigating risks from emerging or reemerging pathogens (Hunter et al., 2011; Schijven et al., 2011). Given the need for credible QMRAs across multiple domains, it is the vision of the authors to make QMRA modelling freely accessible to all interested parties. The inspiration for this software came at the inception of the quantitative microbial risk assessment interdisciplinary instructional institute (QMRA-III). QMRA-III are NIH funded short courses for quantitative and non-quantitative scientists interested in QMRA, a field mostly dominated by physical scientists and engineers.

Dose response modelling is a vital step in the QMRA framework. Without a dose response model, a complete QMRA model is exceptionally difficult to develop if not impossible. Dose response modelling can be considered a niche research field, requiring a solid understanding of microbiology, pathology, mathematics and statistics. The microbiology skills are to understand the protocols used in development and delivery of the inoculum, thus assessing the applicability of the data to dose response modelling. Pathogenesis knowledge is used to determine the relevance and limitations of chosen exposure routes (*e.g.* intracranial versus inhalation) and the limitations of mechanistic assumptions within the model. Advanced mathematics knowledge is needed to understand how to develop approaches to optimize a model and subsequently write the requisite code to perform such algorithms. Cognizance of statistics allows for the inference of a good fit to candidate data, and to determine the confidence associated with applying the model across multiple hosts, pathogen strains, pathogen isolates and exposure routes.

Due especially to its regulatory and public health implications (US EPA, 2000; Petterson et al., 2006a,b), it is vital to make QMRA modelling more accessible to a broader set of expertise. A means of

* Corresponding author. Division of Environmental Health Sciences, College of Public Health, The Ohio State University, 426 Cunz Hall, 1841, Neil Ave, Columbus, OH 43210, USA.
** Corresponding author.
E-mail addresses: weirmarkh@gmail.com (M.H. Weir), jade@msu.edu (J. Mitchell).

http://dx.doi.org/10.1016/j.envsoft.2016.11.011
1364-8152/

Code availability

The **R** source code for dose response optimization and app pseudo code (due to its size) are available at the QMRA wiki (http://qmrawiki.canr.msu.edu/index.php/Dose_Response_Modeling_R_Code). The code as well as the description contains instructions for use. The code and software will work on Windows, Mac and Linux equally well. The user will need to have an updated version of **R** (https://cran.r-project.org/) and their own dose response data, the outline of which can be seen in the software as well as the code description file. The developer is Dr. Mark H. Weir who's contact information can be seen under his affiliation in the author list.

greater accessibility is through instructional programs such as QMRA-III (https://goo.gl/0zYgb5). Other such institutes include: Infrastructure for Health and Ecosystem Risk Assessment (IHERA), Joint Institute for Food Safety and Applied Nutrition (JIFSAN; http://jifsan.umd.edu) and formerly offered under the Center for Advancing Microbial Risk Assessment (CAMRA; www.camra.msu.edu). Unfortunately, these programs are limited by funding availability, the number of participants able to take these courses at any given time, and the amount of time required to instruct QMRA's underlying sciences. This instructional time constraint is no different for the QMRA courses offered in a select few universities. Software such as VizDR (Visual Dose Response) is a first step in allowing for a more effective use of instructional time regarding the specific steps in the QMRA framework, in this case the dose response step. VizDR and similar software will also alleviate the practitioner from developing or running complicated code routines for dose response modelling.

Currently there are a limited number of QMRA software applications that are scenario specific. This is unsurprising due to the scenario driven nature of QMRA (Haas et al., 2014), but, this limits their use outside of the given scenario of development. What can be seen in the following examples of QMRA software is the lack of software for microbial dose response model visualization and optimization. In all of these software packages the dose response model(s) is/are fixed, based on the pathogen(s) chosen or sole pathogen(s) available in the modelling software. Therefore, these packages disallow the user to: choose a dose response model or learn more about dose response modelling in general. Additionally, they do not provide the capacity for the user to develop their own optimized dose response model.

1.1. QMRA software for water

QMRASpot is a QMRA software developed by Kiwa Watercycle Research (KWR). QMRASpot specifically models drinking water systems for the Dutch government (Schijven et al., 2011). This is vital for the Netherlands due to their system not maintaining a chlorine residual (Smeets et al., 2009; Smeets, 2011). Water treatment and distribution system characteristics can be adapted to the user's treatment and distribution system. However, the overall exposure pathway and dose response models are imbedded, unchangeable and cannot be independently visualized in QMRASpot.

1.2. QMRA software for food

The FDA-iRISK is an integrative comparative risk assessment system primarily for food-borne hazards (Chen et al., 2013). iRISK is now expansive over a set of models and scenarios that can be incorporated into a risk model. iRISK limits the users' interactions with the dose response model, simply displaying the dose response model name (*i.e.* exponential or beta Poisson, *etc.*) and their functional forms. iRISK regularly updates the dose response model using expert elicitation from dose response experts. However, the capability to choose, optimize or visualize the dose response models is not available in iRISK.

MicroHibro (http://www.microhibro.com/) is an on-line tool for microbial risk assessment in vegetables and meat products. The tool can be used to carry out a probabilistic exposure assessment based on predictive models of growth, inactivation and cross-contamination (Pérez Rodríguez, 2011). The WHO Food and Agriculture Organization of the United Nations (http://www.fstools.org/) provide QMRA tools for *Cronobacter spp.* in infant formula and for *Campylobacter* and *Salmonella spp.* in chicken meat. Since the tool is limited to these two pathogens there is no choice or interaction with the dose response models.

The Interactive online Catalogue on Risk assessment (ICRA; http://icra.foodrisk.org/) is a catalogue of existing microbial risk assessments. ICRA serves as a resource for risk modelers to use in the development of their own models. ICRA allows users to compare and contrast models for the same pathogen and/or commodity. ICRA is the closest of these four examples of being able to compare and learn more about the dose response models, being a catalogue of risk models. However, we again see an inability to directly visualize current dose response models and no ability for the users to optimize dose response models to their own data.

1.3. Chemical and radiological dose response software

The need for dose-response modelling software was first recognized for chemical risk assessment. Several tools exist, but they do not incorporate the models recommended for use in microbial risk assessment. The U.S. Environmental Protection Agency (EPA) benchmark dose software (BMDS; https://goo.gl/jxSq1d) is used to fit mathematical models to dose response data using established empirical relationships for chemical hazards. Collaborative Drug Discovery (CDD; https://www.collaborativedrug.com) is a proprietary cloud-based tool for high-throughput screening of drugs that fit select dose response models for chemical compounds (Hohman et al., 2009). There is open source software for chemical dose response modelling too. UNISTAT 6.5 (https://www.unistat.com) Statistics Software (London, England, UK) can fit the logit, probit and gompit models. ***DRC*** is an **R** (R Core Team., 2014) dose response modelling package for three and four parameter, sigmodal models including the log-logistic and Weibull (Knezevic et al., 2007).

These tools and packages demonstrate two things: (1) the need for software support for microbial dose response modelling; and (2) the breadth of the various dose response models that are standardized and unique to different domains of study. While software exists for QMRA, they are focused on providing researchers, risk assessors, regulators and decision makers with the capabilities of using a QMRA model already developed. As the dose response model is vital to a QMRA (Weir and Haas, 2011; Haas et al., 2014), the absence of the ability to optimize a dose response model from raw data without consulting with a dose response modelling expert is a limiting step in the QMRA framework. VizDR is a dose response modelling and visualization software intended to end this limitation in QMRA and can be found at the QMRAWiki (https://goo.gl/al7OAB).

2. Methods and materials

2.1. Mechanistic microbial dose response models

A model is only as relevant as its underlying assumptions and methods of derivation. In the case of microbial dose response modelling it is important to derive a model from mechanistic roots. Theoretically any function that is bounded on (0,1) for the