A hierarchical model for probabilistic dose-response assessment of *Bacillus anthracis*

by Jade Mitchell-Blackwood, Patrick L. Gurian, PhD and Mark Weir

Department of Civil Architectural, and Environmental Engineering , Drexel University, Philadelphia, Pennsylvania 19104

Abstract

In this study, a Bayesian statistical approach to fitting dose response parameters for *Bacillus anthracis* was compared to a classical, or frequentist, likelihood-based approach. The Bayesian approach uses a fully probabilistic framework to characterize parameter uncertainty. Parameters describing the susceptibility of individual species are modeled as deriving from a distribution describing the variation of susceptibilities among different species. This allows for estimates of the susceptibility of unobserved species to be determined based on species with observed susceptibilities. This is an attractive approach for bioterrorism risk assessments where the human response to bioterrorism agents can not be assessed directly, and data from surrogate species must be used instead.

Markov Chain Monte Carlo methods are used to develop posterior distributions of exponential dose response model parameters for three different species-rhesus monkeys, guinea pigs, and rabbits. The results from the Bayesian approach were similar to the likelihood-based approach for two of the species – monkeys and guinea pigs, which produced the same mean risk curves. The Bayesian approach also permitted fitting of the rabbit data, for which limited data yielded the likelihood-based approach unworkable. This presents a major advantage of the technique that will allow extrapolation to unobserved species including humans. A major challenge is to properly represent the degree of relatedness of different dose-response experiments. A framework for future research in this area is to consider two attributes for each experiment, microbial strain virulence and host species susceptibility. An autocorrelation function based on degree of difference on these attributes can then be used to represent the relatedness of different dose-response experiment in a quantitative and flexible manner.

Data

Organism / Strain Used	Host Species	Dose (Inhaled Spores)	Number of Test Subjects	Response	Positive Response	Negative Response
Bacillus Anthracis Vollum Strain	Guinea Pig (Altboum, 2002)	20000000	7	Death	7	0
		2000000	8	Death	7	1
		200000	12	Death	10	2
		20000	12	Death	6	6
		2000	8	Death	0	8
		200	4	Death	0	4
Bacillus Anthracis ATCC_6605 Strain	Guinea Pig (Altboum, 2002)	3000000	10	Death	10	0
		300000	10	Death	8	2
		30000	10	Death	3	7
		3000	10	Death	0	10
		300	6	Death	1	5
		30	6	Death	0	6
Bacillus Anthracis Ames Strain	New Zealand White Rabbit (Pitt, 2001)	14600000	10	Death	10	0
		9240000	8	Death	8	0
		19110000	5	Death	5	0
Bacillus Anthracis Vollum Strain	Rhesus Monkeys (Druett, H.A., et. al., 1953)	70320	8	Death	1	7
		77040	8	Death	4	4
		108720	8	Death	5	3
		137520	8	Death	6	2
		155520	8	Death	5	3
		192800	8	Death	3	5
		240000	8	Death	8	0
		300000	8	Death	7	1
		398400	8	Death	8	0

Methods

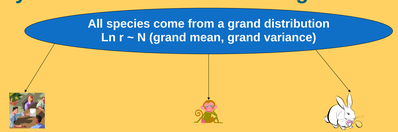
Maximum Likelihood Estimation (MLE) Approach

- The exponential dase-response model was fit to three sets of host-species/ organism-strain groups using the MLE to determine the best fit parameter, *r*.
- Confidence intervals were calculated from a bootstrap resampling technique.

Bayesian Hierarchical Model

- Markov Chain Monte Carlo (MCMC) techniques were used to sample an array of parameter estimates for *r* from four sets of host-species/organism-strain groups using both an informed and an uniformed prior estimate of the distribution
- Mean, median and credible intervals were calculated for each group using this data

Bayesian Hierarchical Modeling



Informed Prior Assumptions

$\ln r \sim n(\mu_{\ln r}, \sigma^2)$

$\ln \mu_{\ln r} \sim n(11.9, 2^2)$

$-2\ln \sigma^2 \sim n(0.67, 0.84^2)$

Dose-Response Model

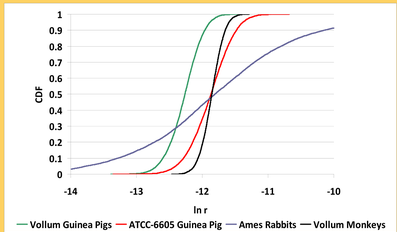
Exponential Dose Response:

$P(d) = 1 - e^{-rd}$

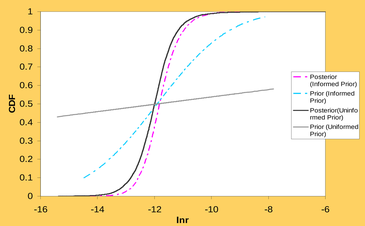
Where:

- P(d) = Probability of effect
- r = pathogen-host survival probability
- d = dose of organisms to host

Results



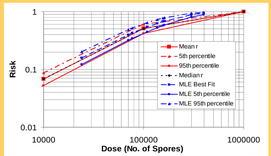
The resulting posterior distributions for each species show similar results except for where there is little data in the case of the Ames Rabbits, which were all killed.



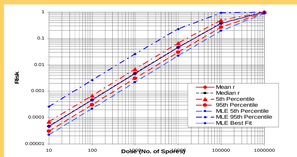
Distribution	Informed	Uniformed
Prior	$\ln\mu_{\ln r} \sim n(-11.9, 2^2)$ $-2\ln\sigma^2 \sim n(-0.67, 0.84^2)$	$\ln\mu_{\ln r} \sim n(-11.9, 20^2)$ $-2\ln\sigma^2 \sim n(-0.67, 0.84^2)$
Posterior	$\ln\mu_{\ln r} \sim n(-11.78, 0.67^2)$	$\ln\mu_{\ln r} \sim n(-11.99, 0.72^2)$

By comparing the prior and posterior distributions we observe that variance is reduced as information is gained from the data. The posterior distributions generated from both the informed and the uniformed prior are similar. This indicates that the specification of the prior has little influence on the result.

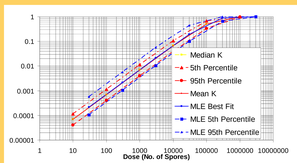
Comparison with Maximum Likelihood Estimation



(a) Vollum Monkeys



(b) Vollum Guinea Pig



(c) ATCC-6605 Guinea Pig

A comparison of the risk (computed using maximum likelihood estimation method and Bayesian hierarchical modeling approach) vs. dose, for three of the host-species/ organism-strain groups is plotted.

Note: There is no plot associated with the rabbits exposed to the Ames strain because all rabbits died, therefore, the maximum likelihood estimation was not possible.

Conclusions

Similar results were observed when the hierarchical model was compared to the MLE approach. Where less observations exist, the Bayesian hierarchical model yields more narrow credible percentiles of risk for individual species. Deviations from the MLE are consistent with the influence of data from other experiments.

When the prior distribution is defined ambiguously, the resulting posterior distribution is very close to the posterior distribution observed from the informed prior, which indicates that there is little influence by prior distribution selection.

Future work

A major challenge is to properly represent the degree of relatedness of different dose-response experiments. A framework for future research in this area is to consider two attributes for each experiment, microbial strain virulence and host species susceptibility. An autocorrelation function based on degree of difference on these attributes can then be used to represent the relatedness of different dose-response experiment in a quantitative and flexible manner.

Extrapolation to unobserved data sets, including humans may be possible by weighting data sets of species closely related to humans.

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For further information

Please contact jade@drexel.edu.
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