Dose-response Time Modeling

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Motivation

- In microbial risk assessment, it is desirable to take the time factor into account for consequence assessment from bioterrorist and other microbiological exposure.
- Microorganisms have the ability to replicate in the host species. This resulting amplified body burden may be the ultimate cause of the biological effect. This is a time-dependent process.
- -Chemicals: the received dose = ultimate amount
- -Micro-organisms: the ultimate dose can be greater than the received

Challenge

- Classical dose-response model

  -predicting the overall risk from exposure to a given dose

  -no description about the duration over which cases may occur after the exposure

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

$$P(d) = 1 - \left[1 + \left(\frac{d}{N_{50}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

Objective

- Dose-response models will be modified with the factor of time to predict not only the ultimate response, but the response as a function of time post inoculation (TPI).

Data and fitting method

- Survival dose-response data

  -Graded dose

  -Total number/number with response per dose group

  -Time to response for each animal with response

- Maximum likelihood estimation (MLE)

  (Haas *et al*., 1999)

  -Determine the acceptable fit: compare the deviances with $\chi^2_{0.95,df}$

Summary of survival data

- Response endpoint: death
- Host: animals
- Pathogens:

  -*Bacillus anthracis,* 7 data sets

  -*Yersinia pestis*, 6 data sets

  -*Francisella tularensis*, 9 data sets

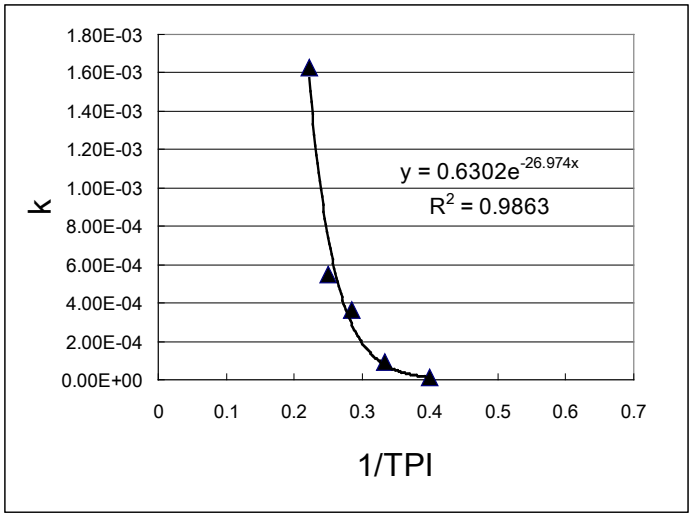
MLE fitting for individual day

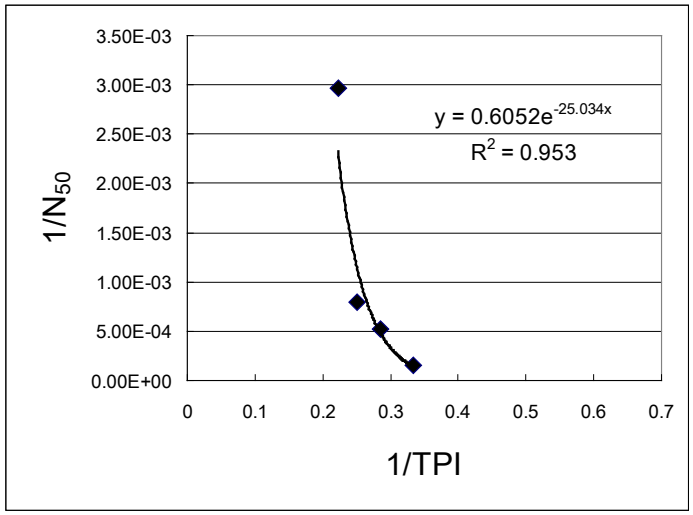
The exponential and beta-Poisson model were fitted to the response on each individual day and the optimized parameters were obtained

		Cumulative Number Dead at Given Time Post Inoculation (TPI)														
No. Animals	**dose (CFU)**	**Time Post Inoculation (d)**														
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
10	**1**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	**10**	0	0	0	1	2	2	2	2	2	3	3	3	3	3	3
10	**100**	0	0	0	0	3	5	6	6	6	6	6	6	6	6	6
10	**1000**	0	0	0	4	9	9	9	9	9	9	9	9	9	9	9
10	**10000**	0	0	0	2	10	10	10	10	10	10	10	10	10	10	10

Exploration of functional dependency on time

- Plot the optimal parameter vs TPI
- Determine the candidate trend





Exponential relationship between (a) k and reciprocal TPI, (b) $1/N_{50}$ and reciprocal TPI, for C57BL/6 mice infected by *Yersina pestis* CO92 strain via intranasal route (Huang and Haas, 2009)

Modified dose-response model

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

$$P(d) = 1 - \left[1 + \left(\frac{d}{N_{50}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

$$k = e^{(k_0 / TPI + k_1)}$$

$$N_{50} = e^{(j_0 / TPI + j_1)}$$

$$P(d) = 1 - e^{-e^{(k_0 / TPI + k_1)} d}$$

$$P(d) = 1 - \left[1 + \left(\frac{d}{e^{(j_0 / TPI + j_1)}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

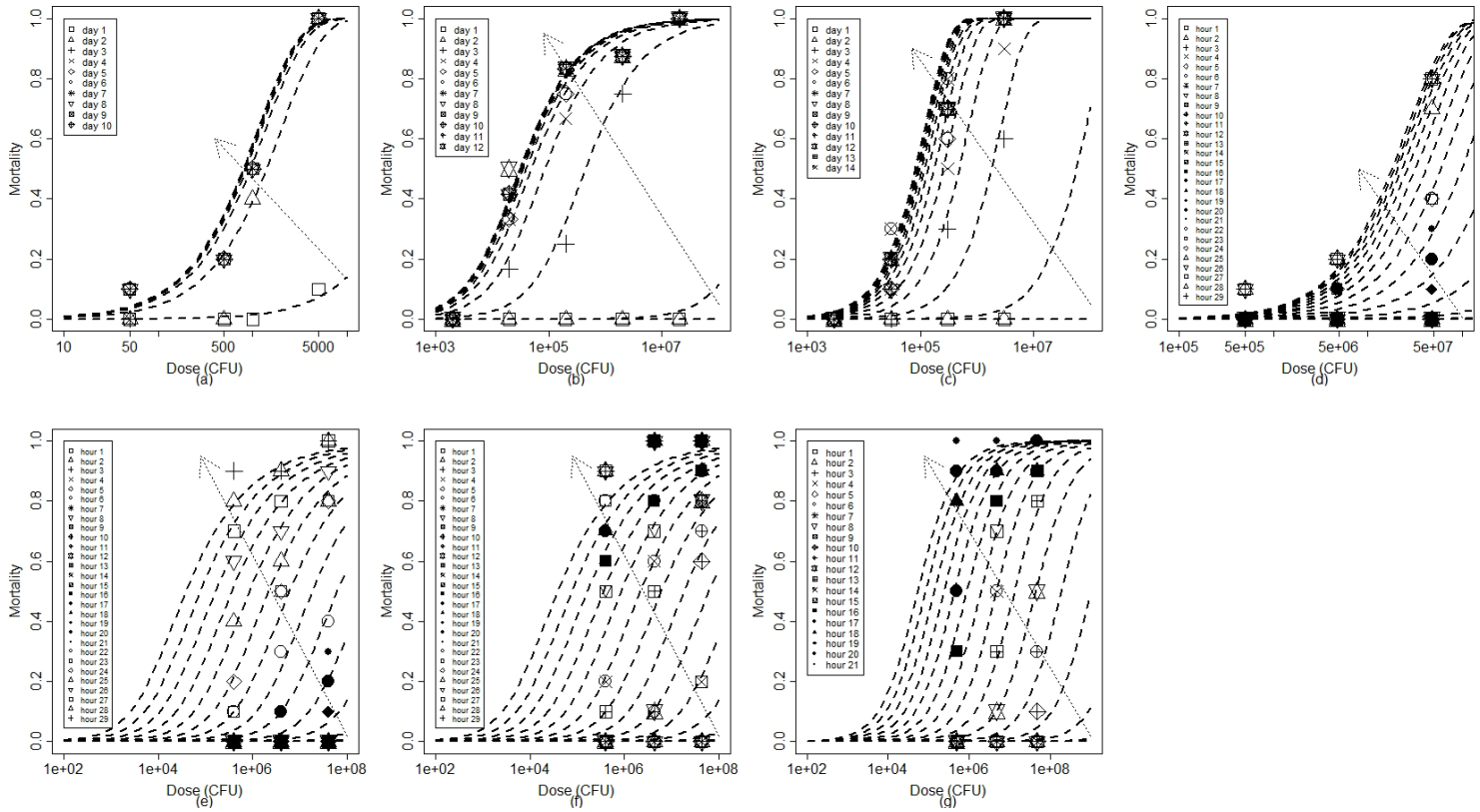
$$k = e^{[k_0 / (TPI)^{k_2} + k_1]}$$

$$N_{50} = e^{[j_0 / (TPI)^{j_2} + j_1]}$$

$$P(d) = 1 - e^{-e^{(k_0 \times (TPI)^{k_2} + k_1)} d}$$

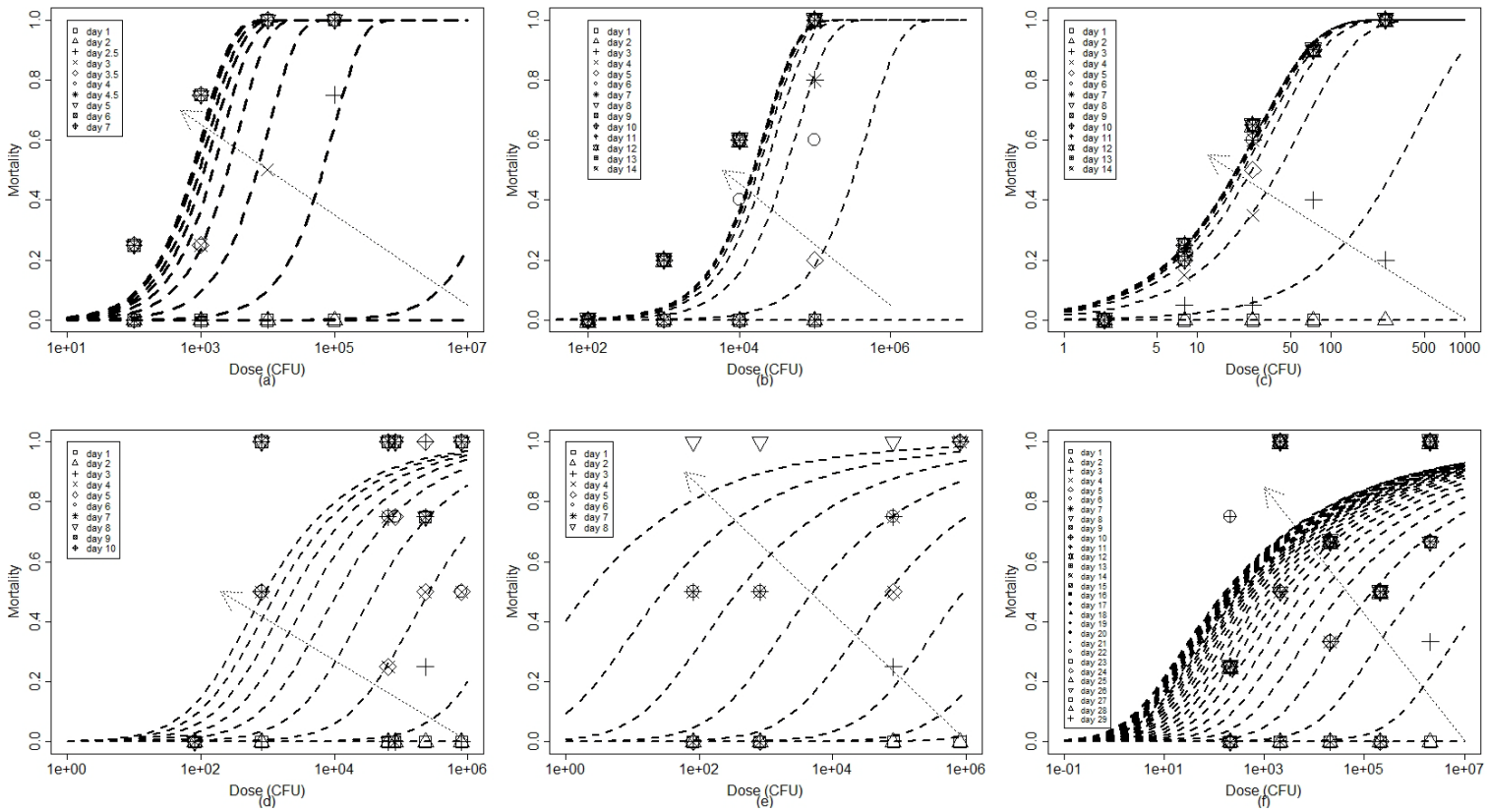
$$P(d) = 1 - \left[1 + \left(\frac{d}{e^{(j_0 \times (TPI)^{j_2} + j_1)}}\right) \cdot \left(2^{1/\alpha} - 1\right)\right]^{-\alpha}$$

MLE Fits for *B. anthracis* infection



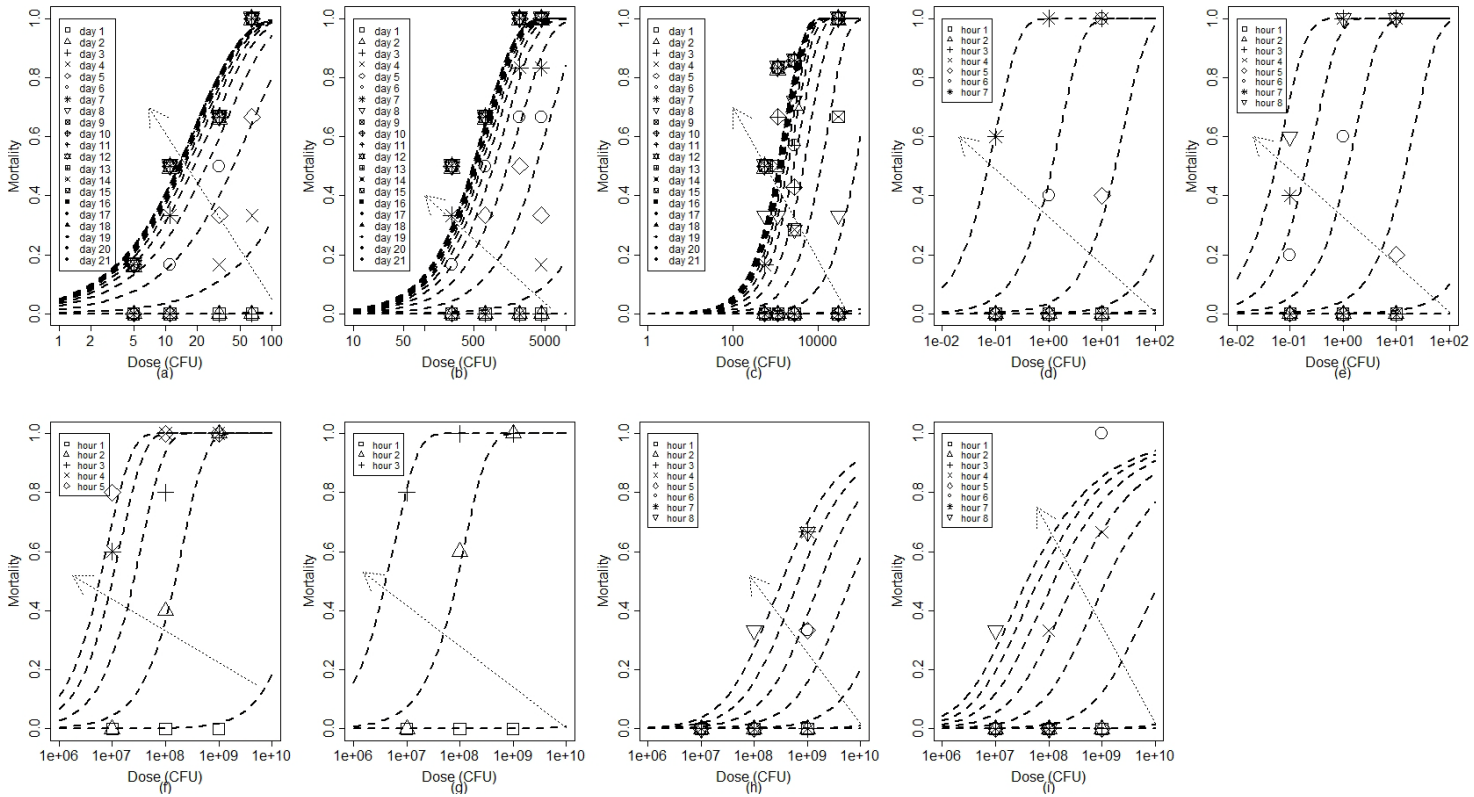
(a) mice intratracheally infected with *B. anthracis* Ames strain, (b)-(c) guinea pigs intranasally infected with Vollum and ATCC 6605 strain, (d)-(g) mice intraperitoneally infected with Pasteur No. 2 spore vaccine strain replicate 1 and 2 and Vollum strain replicate 1 and 2 (Huang and Haas, 2009).

MLE Fits for *Y. pestis* infection



(a)-(b) mice intranasally infected with *Y. pestis* CO92 and KIM D27 strain, (c) mice intraperitoneally infected with CO92 strain, (d)-(f) Langurs (*Presbytis entellus* and *Presbytis cristata*) and grivets subcutaneously infected with 195/P strain (Huang and Haas, 2009).

MLE Fits for *F. tularensis* infection



Monkeys inhalationally infected with (a) 2.1 μm, (b) 7.5 μm, and (c) 12.5 μm aerosol particles of SCHU S-4 strain of *F. tularensis*; white mice injected with (d) No.55 strain and (e) No.56 strain; white rats injected with (f) No.55 strain and (g) No.56 strain; domestic rabbits injected with (h) No.55 strain and (i) No.56 strain (Huang and Haas, 2009).

Summary of fitting results

- The modified beta-Poisson models provided statistically acceptable fits for all the tested data sets under the criteria described earlier, while the modified exponential models provided significantly acceptable fits for most of the data sets.

Conclusion and significance

- Time-dose-response models described the development of animal infectious response over time and represented observed responses accurately.
- The success of fitting to disparate pathogens with different characteristics indicates that TPI models are of an adequate flexibility.
- The outcome may be used for an improved post-exposure decision making or as a component to better assist epidemiological investigations.

Acknowledgements

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References

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