Comparing methods for estimating parasite-induced host mortality from distributional data: implementation and limitations

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Abstract

TODO

Introduction

Infectious agents can have major impacts on animal populations through changing population dynamics and stability, altering predator-prey interactions, and even causing species' decline and extinction. Accurately estimating the impact of these infectious agents in wildlife is critical to both understanding what regulates host and parasite populations and making predictions about disease transmission. The impact of pathogens, such as rabies(), bovine TB(), and rinderpest(), is typically quantified based on the presence or absence of disease, and does not account for the number of infectious agents present. Although sufficient for many bacterial and viral agents that reproduce within a host, for macroparasites, hosts cannot be simply categorized as infected and uninfected because pathology is linked to the intensity of infection (Anderson and May 1978). Helminths exhibiting this intensity dependent pathology have significant impacts on human health (), domestic livestock economics (), wildlife survival (). And, while it is generally

assumed that some fraction of wild host populations must succumb to parasitic infections, it is notoriously difficult to actually quantify parasite-induced host mortality (PIHM) in wild animal populations. [more]

Ideally, parasite-induced host mortality would be quantified by experimentally infecting and tracking individual hosts in the wild population; however, for logistical and ethical reasons this method is rarely feasible. Data on parasite intensity is much easier to collect and has often been used to identify the presence PIHM (cite studies) and quantify the relationship between infection intensity and host mortality (cite studies).

Crofton (1971) first proposed that PIHM could be identified by comparing the observed parasite distribution in the host population to the distribution predicted in the absence of parasite-induced host mortality. This method ("Crofton Method") assumes that, prior to host mortality, parasites are distributed in the host population following a negative binomial distribution; however, as intensity dependent pathology removes heavily infected hosts from the population, the tail of the distribution is truncated. Mortality is assumed to not occur in hosts with low intensity infections, thus by iteratively fitting a negative binomial distribution to hosts with lower and lower parasite loads, and comparing the tail end of this predicted distribution to the observed parasite data, one could determine both whether PIHM was occurring and the parasite distribution in the host population prior to parasite induced mortality. We give a thorough description and implementation of the Crofton Method in *Supplementary Information (SI)* 1 and discuss the validity of its assumptions in the *Discussion*.

The Crofton Method may be able to detect the presence of PIHM however, quantifying the relationship between infection intensity and survival probability is more complicated. Adjei *et al.* (1986) suggested that these values could be quantified by using the Crofton Method to first estimate the pre- mortality parasite distribution and then, using those parameters, calculate the probability of host

survival with increasing parasite load. To do this, Adjei *et al.* (1986) modeled host survival as a logistic function and then used a binomial generalized linear model (GLM) to estimate the logistic parameters. These methods appeared to provide an estimate the parasite intensity at which 50% of hosts exhibit PIHM (), as well as the unmeasurable fraction of the population that was lost (SI for adjei method details and extended discussion of issues?). However, to implement this method the observed data must be modified to fit the binomial GLM framework and subjectively binned when mean infection intensity is high or sample sizes are small.

After 30 years, and despite clear limitations (McCallum 2000), these methods (particularly the Crofton Method) are still discussed among parasitologists and are the primary techniques for examining population level impacts of parasitism using parasite intensity data. In these methods, PIHM can only be identified by visually examining plots and, with no clear decision rule; it can be difficult to determine the significance of PIHM across different host-parasite systems. The survival function produced by the Adjei Method offers one solution; however, this method requires manipulating the original data and has never been thoroughly tested.

Estimating parasite impacts on host population using intensity data should only be done if methods exist to permit unbiased and accurate estimates of PIHM. In this study, we first propose a novel likelihood method for calculating PIHM. We next use simulations to compare this likelihood method with previous Adjei method to (1) test the ability to detect occurrence of PIHM and (2) estimate lethal parasite load (LD_{50}) and associated survival function. We then apply both methods to real datasets previously used in PIHM analyses and compare results. And, finally, we discuss the limitations of inferring PIHM from distributional data and whether any method for inferring PIHM has a place in quantitative parasitology.

Methods

A novel, likelihood method for estimating PIHM

Here we propose an alternative approach using a likelihood method that does not require binning or data alteration, potentially reduces the number of parameters to be estimated, and allows the significance of PIHM to be estimated using standard statistical techniques.

As with all previously proposed methods for estimating PIHM, the Likelihood Method first assumes that the pre-mortality distribution follows a negative binomial distribution $g(x; \mu_p, k_p)$. The second assumption is that the host survival function takes the form of a logistic curve given by

$$h(x|a,b) = h_x = \frac{e^{a-b\log(x)}}{1+e^{a-b\log(x)}} \tag{1}$$

With these two explicit assumptions, the Likelihood Method estimates the 4 parameters μ_p, k_p, a, and b.

To estimate these parameters, we first define a probability distribution that gives the probability of having a parasite load of x parasites conditional on host survival. Using standard rules of conditional probability this distribution can be written as

$$P(x|\text{survival}) = \frac{P(\text{survival}|x) * P(x)}{P(\text{survival})} \tag{2}$$

One can see that $P(\text{survival}|x)$ is the survival function $h(x; a, b)$, $P(x)$ is the pre-mortality parasite distribution $g(x; \mu_p, k_p)$ and $P(\text{survival}) = \sum_{x=0}^{\infty} P(\text{survival}|x) * P(x) = \sum_{x=0}^{\infty} h(x; a, b) * g(x; \mu_p, k_p)$. Therefore equation 2 can be written as

$$P(x|\text{survival}) = \frac{h(x; a, b) * g(x; \mu_p, k_p)}{\sum_{x=0}^{\infty} h(x; a, b) * g(x; \mu_p, k_p)} \tag{3}$$

Using this probability distribution, one can then find the parameters μ_p, k_p, a, and b that maximize the likelihood of an observed host-parasite dataset. Alternatively, one could apply the Crofton Method to estimate μ_p and k_p and then find the maximum likelihood estimates of a and b and the corresponding LD_{50}.

To estimate that significance of PIHM in a host-parasite system, a likelihood ratio test can be used in which the full model is given by equation 3 and the reduced model is given by a negative binomial distribution. If PIHM is not significant in the system, the resulting likelihood ratio statistic should approximately follow a χ^2 distribution with degrees of freedom equal to 2. We provide the code for implementing this Likelihood Method in SI 3.

0.1 Evaluating the likelihood and Adjei Methods

Question 1: Can we detect PIHM?

To test the ability of the Adjei Method and the Likelihood Method to identify whether or not PIHM was occurring in a system, we randomly generated data using the following procedure. First, we drew N_p randomly infected hosts from a negative binomial distribution with parameters μ_p and k_p. This represented the dataset observed before mortality. Second, we chose values of a and b and calculated the probability of survival for all N_p hosts using equation 1. Third, we drew N_p random numbers from a uniform distribution between 0 and 1 and if host survival probability was less than this random number, the host experienced parasite-induced mortality. The surviving hosts comprised the dataset that would be obtained in the field, after PIHM.

Using both the pre-mortality and post-mortality simulated datasets, we assumed that the values of N_p, μ_p, and k_p were known and tested the ability of both methods to correctly determine whether or not PIHM was occurring. While this

scenario is unrealistic because the parameters N_p, μ_p, and k_p are always unknown, we implemented this scenario as a baseline to establish the efficacy of the methods independent of the estimates of N_p, μ_p and k_p. For the Adjei Method, N_p, μ_p, and k_p are estimated using the Crofton Method, while μ_p and k_p in the Likelihood Method can be estimated jointly with a and b or via the Crofton Method. If a method could not correctly predict whether or not PIHM was occurring under these idealistic conditions, we considered this strong evidence of the unreliability of this method.

We used three different values of μ_p (10, 50, 100) and for each μ_p we examined three different survival functions that had graduate, moderate, and steep decreases in host survival with increasing parasite intensity (Figure 1). For a given μ_p, each survival function had the same LD_{50} ($[\mu_p = 10,\ LD_{50} = 7.39]$, $[\mu_p = 50,\ LD_{50} = 35.57]$, $[\mu_p = 100,\ LD_{50} = 77.3]$), but different values of a and b. We examined each μ_p-survival function pair at three levels of parasite aggregation, $k_p = 0.1$, 0.5, and 1 — realistic values of parasite aggregation in natural populations (Shaw *et al.* 1998). For each of these parameter combinations we simulated 150 datasets and tested the probability of each method incorrectly identifying PIHM in the pre-mortality dataset (Type I error) and correctly identifying PIHM in the post-mortality dataset (power). For each method, we used a likelihood ratio test to determine whether the full model with PIHM provided a significantly better fit than the reduced model without PIHM at significance level $\alpha = 0.05$. We tested each parameter combinations for pre-mortality population sizes of $N_p = [50, 100, 200, 300, 400, 500]$. N_p is not technically the sample size on which the methods are being tested on the post-mortality data because PIHM reduces N_p for each simulated dataset. We therefore used the average number of surviving hosts over all 150 simulations for a given parameter combination as our measure of sample size in the power simulations.

Question 2: Can we estimate fatal parasite intensity and the host survival function?

To compare the ability of the Adjei Method and the Likelihood Method to recover the LD_{50} and the parameters a and b of the survival function, we used the same simulation procedure and parameter combinations described above. For each parameter combination we simulated 150 datasets, estimated a, b, and LD_{50} and calculated the standardized bias and precision (Walther & Moore 2005) for these estimates over varying pre-mortality host population sizes N_p = [300, 500, 1000, 2000, 5000, 7500, 10000]. We used the average number of surviving hosts over all 150 simulations for a given parameter combination as our measure of sample size. Because parameters a and b showed similar patterns of bias and precision, we only show the results for a.

Application to real data

We tested the ability of the Adjei Method and the Likelihood Method to identify PIHM in 6 host-parasite datasets given in Crofton (1971) and 4 datasets given in Adjei *et al.* (1986) (Table 1). In the Crofton (1971) datasets, the host was the snail *Gammarus pulex* which acts as the intermediate host for the acanthocephalan *Polmorphus minutus*. In the Adjei *et al.* (1986) datasets, the hosts were two species of lizard fish *Saurida tumbil* and *Saurida undosquamis* that were infected by the cestode *Callitetrarhynchus gracilis*. Males and females of both fish species were considered separately.

In both studies, the authors reported PIHM in some of the datasets and we test whether the Adjei Method and/or the Likelihood Method also predicted PIHM. For the 6 datasets from Crofton (1971), we truncated the data at 4 parasites, applied the Crofton Method to estimate the pre-mortality distribution, and then ran the Likelihood Method and Adjei Method using these pre-mortality

parameters. For the Adjei *et al.* (1986) datasets, we followed the same procedure as the authors and first truncated the data at 2 parasites and then fit the Crofton Method for the female fish of both species. Then, following the original authors' methods, we parameterized the male pre-mortality distributions for each species with the results from the females. Finally, we applied the Adjei Method and the Likelihood Method to determine whether or not PIHM was significant for these species and compared our results to those given by the authors. All fitting to data was done with the Python code provided in SI 3.

Results

Question 1: Detecting presence of PIHM

The Adjei Method showed highly inflated Type I error rates (i.e. falsely detected PIHM) for all parameter combinations that we considered (Figure 2; SI2 Figs 1, 2). This method also showed the unintuitive pattern of Type I error rate decreasing as sample size decreased. This pattern is due to the issue of binning discussed in the *Introduction* and *SI X*. For small samples sizes, the applicability of the Adjei Method is compromised without binning the observed data in some way. In contrast, the Likelihood Method showed a Type I error rate at or near the pre-set level of 0.05 for all parameter combinations and sample sizes considered.

The ability of the Adjei Method to detect PIHM given that it was occurring in a system (i.e. the power) was close to 1 for larger sample sizes and tended to decrease as sample size decreased (Figure 2; SI2 Figs 1, 2). The Likelihood Method had a power close to one for all parameter combinations and sample sizes considered. With gradual survival functions, the power of the Likelihood Method decreased slightly for small samples sizes (solid black lines; Figure 2, SI2 Figs 1, 2).

Question 2: Estimating the LD_{50} and survival function

The Likelihood Method gave asymptotically unbiased estimates of the LD_{50} for all combinations of parameters examined in this study (Figure 3, SI2 Fig 3, 4). Even for small sample sizes (< 500 hosts), the Likelihood Method's estimate of LD_{50} was largely unbiased, with small biases occurring for host survival functions that were gradual. The precision of the Likelihood Method's LD_{50} estimates decreased (increasing coefficient of variation) as sample size decreased for all parameter combinations we examined (Figure 3, SI2 Fig 3, 4).

The Adjei Method always produced biased estimates of the LD_{50} across all parameter combinations (Figure 3, SI2 Fig 3, 4). For $\mu_p = 10$, the LD_{50} estimates from the Adjei Method were largely unbiased for large samples sizes, but showed increasing bias as sample size decreased, particularly for steep survival functions. As μ_p increased, the Adjei method produced biased estimates of LD_{50} across all sample sizes, with bias increasing as sample size decreased (SI2 Fig 3, 4). The LD_{50} estimates from the Adjei Method showed large decreases in precision occurring for the steepest survival function across all values of μ_p (Figure 3, SI2 Fig 3, 4).

In terms of the host survival function, the Likelihood Method gave asymptotically unbiased estimates of a as sample size increased for all parameter combinations considered (Figure 4, SI2 Fig 5, 6). However, as sample size decreased, the Likelihood Method tended to produce severely biased estimates of a. This was generally more pronounced for steeper survival functions and more aggregated pre-mortality distributions (e.g. Figure 4). The Adjei Method produced biased estimates of a across all sample sizes, with the bias consistently being larger when the survival function was steeper. The bias of the Adjei Method's estimate of a also increased as μ_p increased (Figure 4, SI2 Fig 5, 6).

Application to real data

Of the 10 datasets we considered, the previous authors visually detected PIHM in 7 of them (Table 1). The Likelihood Method parameterized from the pre-mortality parameters of the Crofton Method detected significant PIHM in 6 of these 7 datasets at a significance level of 0.05. The only dataset in which the Likelihood Method did not detect a significant effect of PIHM was the Adjei dataset for female *S. tumbil*. For this dataset there was a marginally significant effect of PIHM ($\chi^2_{df=2} = 5.34; p = 0.069$).

The Adjei Method detected PIHM in 9 of the 10 datasets (Table 1), showing that the Adjei Method has a very high Type I error rate.

Discussion

We show that the Adjei Method, the only currently proposed method to estimate the host survival function and the LD_{50} from observational data, has some serious methodological problems that result in biased estimates even under the most idealistic conditions. Moreover, we show that the Adjei Method will often detect PIHM even when it is not present and for small, realistic sample sizes the Adjei Method behaves erratically; a consequence of the need to subjectively bin the data in order to predict parasite intensity classes with at least one host.

In contrast, our novel likelihood method has a Type I error rate close to the pre-set level of $\alpha = 0.05$ and high power for detecting PIHM for realistic host samples sizes. Moreover, is asymptotically unbiased when estimating the host-survival function for all of the parameter space that we explored and we found that it produces unbiased and precise estimates of the LD_{50} across all samples sizes we considered. However, this method does produce seriously biased estimates of the host survival function (a and b) as sample size decreased . The bias was most

severe for steep host survival functions, due to large changes in the values of a and b only slightly changing an already steep survival function. Given these results, neither the Likelihood Method nor the Adjei Method could confidently recover the exact shape of the host survival function for small, realistic sample sizes.

We also fit both the Likelihood Method and the Adjei Method to empirical data to determine whether they could detect PIHM that had been previously reported based on visual assessments. Consistent with our simulation results, we found that the Adjei Method tended to detect PIHM where it had not been previously reported, while the Likelihood Method's detection of PIHM was consistent with previously reported PIHM in a given dataset. Taken together, these results suggest that the Adjei Method is fundamentally flawed and we recommend using the Likelihood Method for detecting PIHM and describing attributes of the host survival function.

While we have improved upon the previously existing methods for answering questions about PIHM, we cannot belie the fact that estimating PIHM from observational data alone is ladened with assumptions and difficulties (McCallum 2000). The most fundamental assumption of all methods for estimating PIHM is that the shape of the pre-mortality host-parasite distribution is known and follows a negative binomial distribution. While there is substantial empirical and theoretical evidence to justify the use of the negative binomial distribution as the pre-mortality distribution for macroparasites across hosts (Calabrese *et al.* 2011; Anderson & Gordon 1982; Shaw *et al.* 1998), it is widely recognized that different processes can lead to a variety of distributions of parasites across hosts (Isham 1995; Grenfell *et al.* 1995; Wilson *et al.* 2002; Duerr *et al.* 2003). However, the critical assumption of the pre-mortality distribution is not that the processes leading to the pre-mortality distribution generate a negative binomial distribution, but rather that the pre-mortality distribution is well-fit by a negative binomial distribution. The extreme flexibility of the negative binomial distribution makes it

a reasonable candidate distribution for the pre-mortality distributions. Therefore, we do not see this assumption as central problem in any of the proposed methods.

However, to use the pre-mortality distribution to infer whether or not the PIHM is occurring in a system requires an explicit assumption about the host survival function and the shape of the post-mortality distribution. Regarding the host-survival function, all currently proposed methods of PIHM assume that the host-survival function is such that uninfected individuals and individuals with low parasite intensity experience essentially no PIHM. Lanciani & Boyett (1989) illustrated the importance of this assumption by showing that when hosts experienced a linear decrease in survival probability the Crofton Method could not detect PIHM. As the most fundamental models of host-parasite dynamics assume a linear decrease in host survival probability with increasing parasite intensity (Anderson & May 1978), the failure of these methods to detect this relationship is a significant disconnect between empirical and theoretical disease ecology. However, empirical work has shown that non-linear functions of host survival are not uncommon in host-parasite systems (Benesh 2011), so this assumption alone does not preclude the use of PIHM methods on empirical data.

Regarding the shape of the post-mortality distribution, all of these methods require that the post-mortality distribution be significantly different from a negative binomial distribution. This is necessary because none of the above methods will be able to detect PIHM if a negative binomial distribution is an adequate fit to the post-mortality distribution. This is simply because there will be no need for a more complex model (either truncation of the negative binomial or the model given in equation 3) if a negative binomial distribution already fits the data. As many observed host-parasite distributions are not significantly different from a negative binomial distribution, there may be limited cases where these PIHM methods can even be considered.

Finally, all of these methods assume that the truncation of a negative

binomial distribution is due to PIHM, but previous studies have shown that a variety of other processes can lead to the truncation of a negative binomial distribution such as within host parasite density-dependence, age- dependent variation in host resistance and heterogeneous rate of infection (McCallum 2000; Anderson & Gordon 1982; Rousset *et al.* 1996). Therefore, even detecting "significant" PIHM in a dataset does not mean that PIHM is cause of the truncation.

Given these numerous caveats, is there a place in parasitology for methods that estimate PIHM from distributional data? We are in agreement with Lester (1984) that, at the very least, methods for estimating PIHM can provide preliminary insight into whether or not PIHM is worth further exploration. However, we stress that these methods should only be used as an exploratory tool when assessing the role of PIHM in a system and potential users should critically evaluate whether they think they have a large enough sample sizes and an appropriate host survival function/post-mortality distribution for the methods developed in this paper to be applicable. Even if they are applicable, inferring PIHM from distributional data is no substitute for field or laboratory experiments and/or in depth understanding of the natural history of the host-parasite system under consideration.

Acknowledgments

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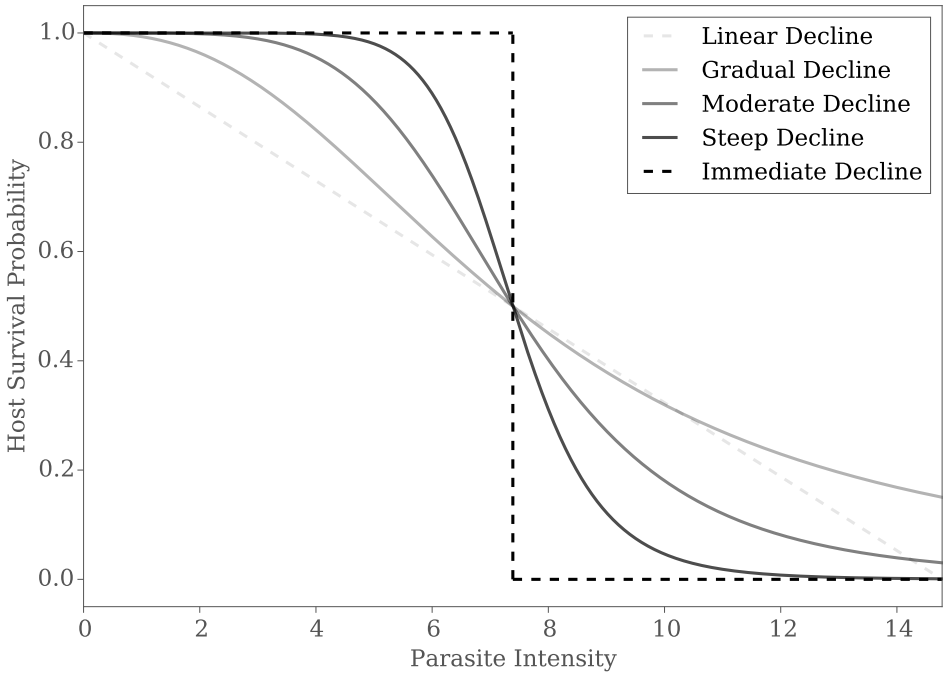

Figure 1: Five potential shapes for a host-survival functions. PIHM should be easier to detect for steeper host survival functions (Lanciani & Boyett 1989), but we may expect the bias in the parameter estimates to increase as it becomes increasingly difficult to distinguish between steep survival functions.

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Table 1: Comparison of the PIHM predictions of previously used host-parasite datasets to those given by the Adjei Method and the Likelihood Method. The first column specifies the identity of the dataset, the second column specifies whether or not the author indicated that PIHM was occurring in the system, the third column indicates whether or not the Likelihood Method with parameters from the Crofton Method detects significant PIHM, and the final column indicates whether the Adjei Method with pre-mortality parameters estimated from the Crofton Method detects PIHM. If a method detected significant PIHM the predicted LD_{50} is given in parentheses

Data Set (sample size)	Author detected PIHM?	Likelihood Method?	Adjei Method?
Crofton, Station 1 ($n = 538$)	Yes	Yes (7.27)	Yes (9.33)
Crofton, Station 2 ($n = 507$)	Yes	Yes (6.92)	Yes (14.95)
Crofton, Station 3 ($n = 633$)	Yes	Yes (5.93)	Yes (5.98)
Crofton, Station 4 ($n = 486$)	No	No	Yes (7.99)
Crofton, Station 5 ($n = 276$)	No	No	Yes (10.58)
Crofton, Station 6 ($n = 191$)	No	No	No
Adjei, *S. tumbil* female ($n = 446$)	Yes (5.7)	No	Yes (6.37)
Adjei, *S. tumbil* male ($n = 452$)	Yes (3.4)	Yes (3.42)	Yes (3.66)
Adjei, *S. undosquamis* female ($n = 2573$)	Yes (3.2)	Yes (3.04)	Yes (3.11)
Adjei, *S. undosquamis* male ($n = 2440$)	Yes (1.8)	Yes (1.83)	Yes (1.78)

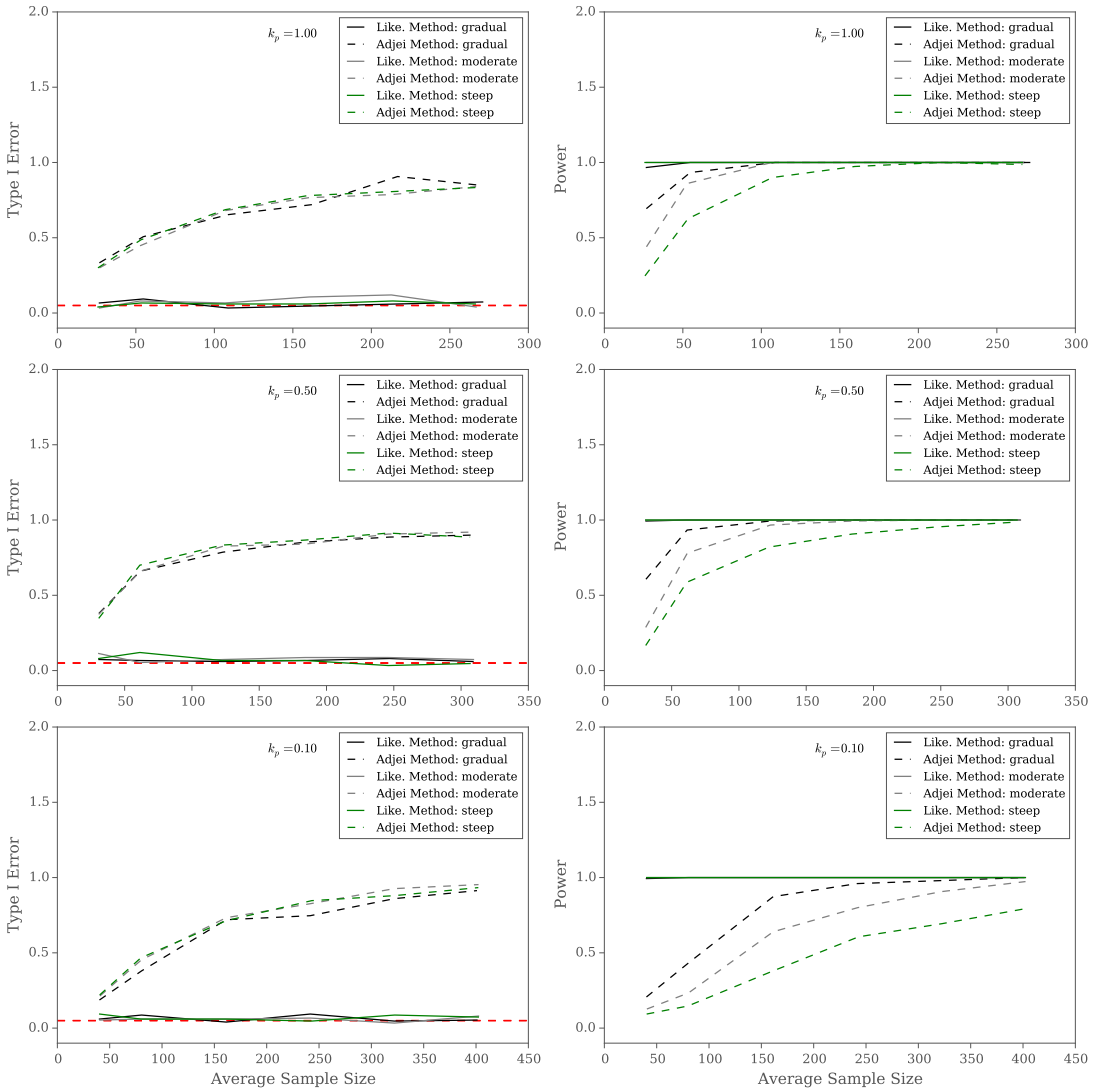

Figure 2: The Type I error rate and the power of the Likelihood Method (solid line) and the Adjei Method (dashed lines) when $\mu_p = 10$ for various shapes of the host survival function and levels of aggregation k_p. The first column gives the Type I error rate of each method for falsely detecting PIHM when none is present. The red line gives the the pre-set Type I error rate of $\alpha = 0.05$. The second column gives the power of a given method to detect PIHM when it is actually occurring.

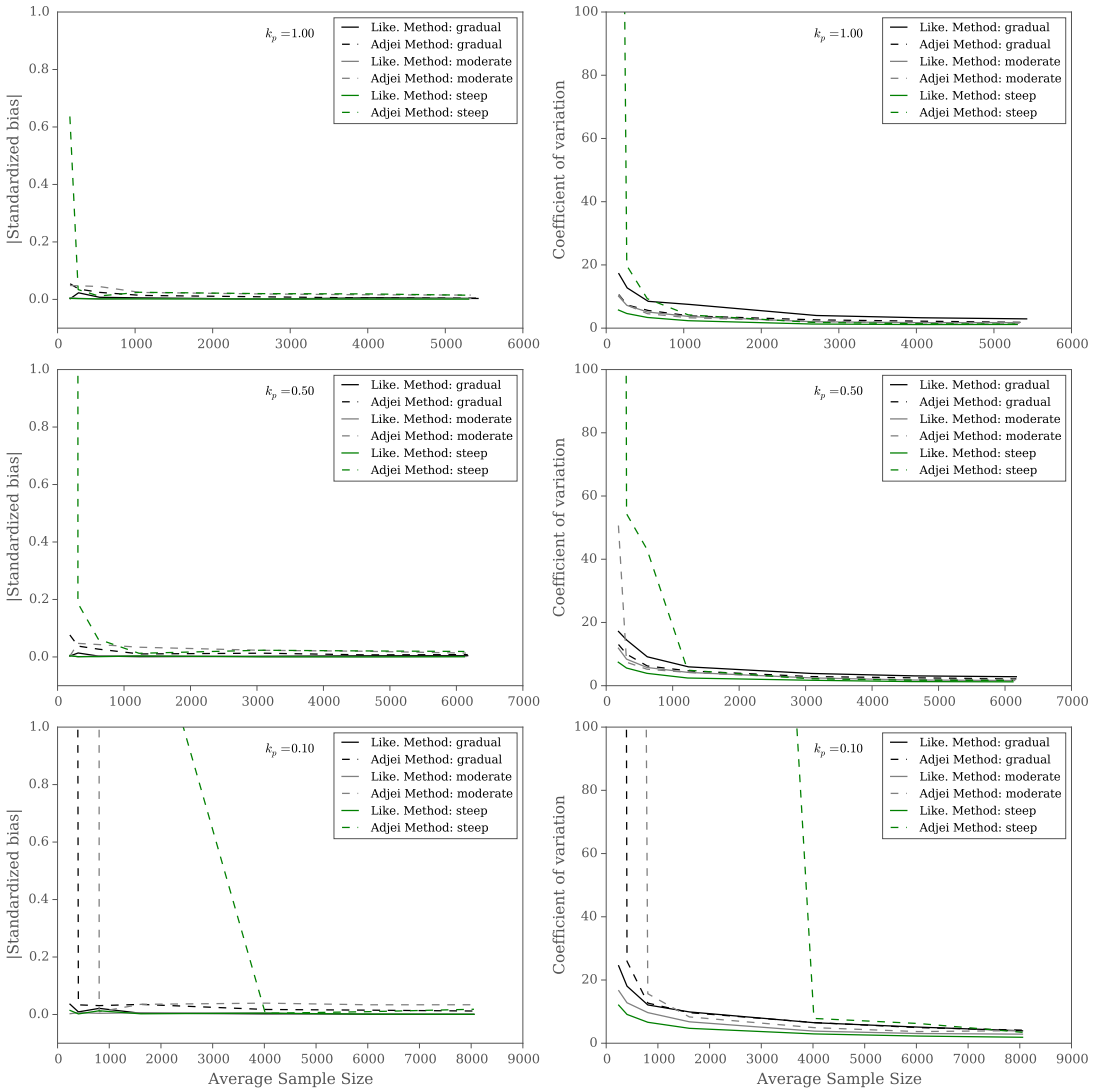

Figure 3: The bias and the precision of the Likelihood Method (solid line) and the Adjei Method (dashed lines) when $\mu_p = 10$ for various shapes of the host survival function and levels of aggregation k_p when estimating LD_{50}. The first column gives the bias of each method's LD_{50} estimate over 150 simulations. The second column gives the precision of each method's LD_{50} estimate over 150 simulations.

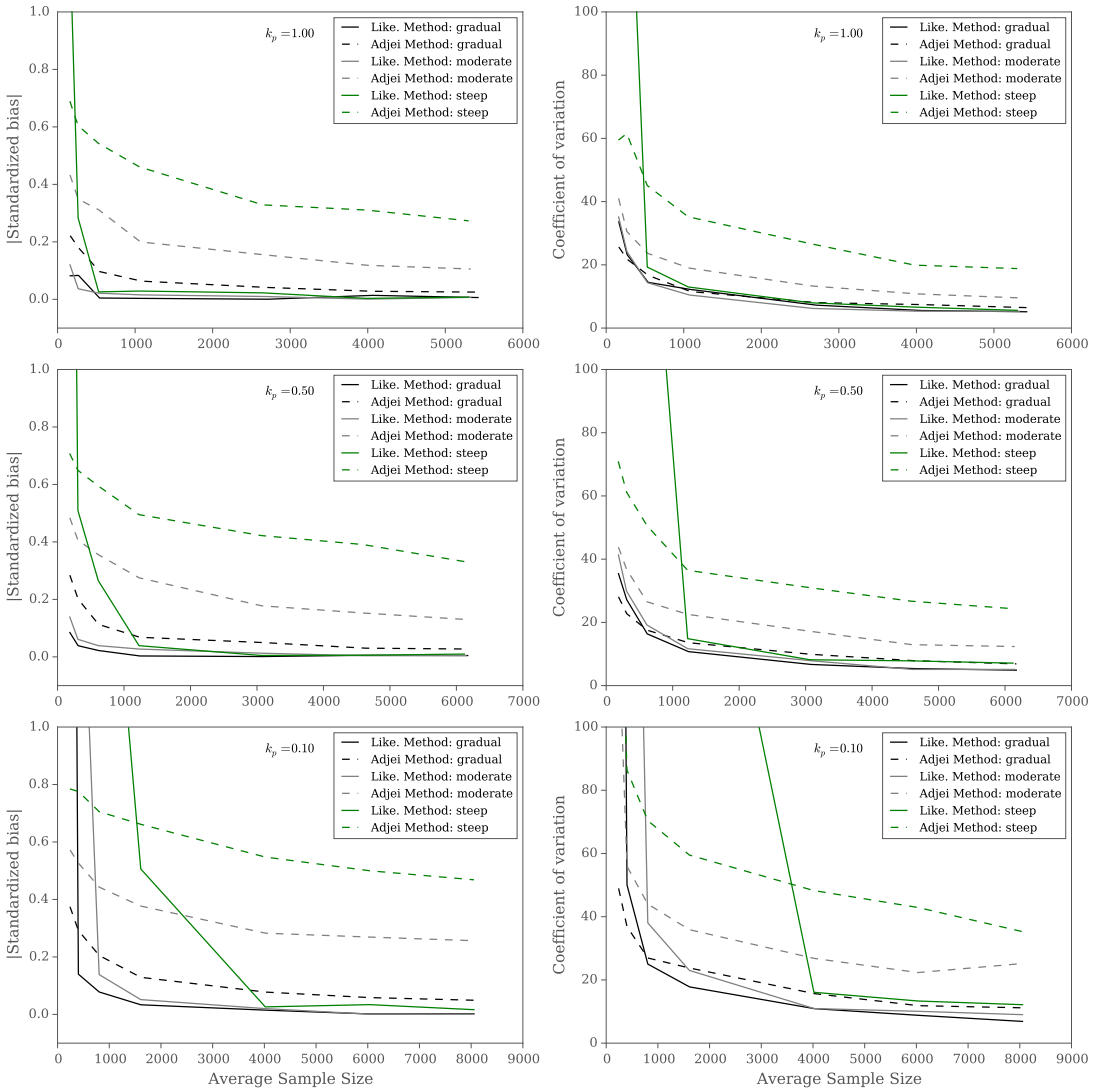

Figure 4: The bias and the precision of the Likelihood Method (solid line) and the Adjei Method (dashed lines) when $\mu_p = 10$ for various shapes of the host survival function and levels of aggregation k_p when estimating the a parameter of the host survival function. The first column gives the bias of each method's a estimate over 150 simulations. The second column gives the precision of each method's a estimate over 150 simulations.