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looking at a wide variety of survival models, we obtained a good characterization for the hazard and survival function of our host study organism, the fall armyworm *Spodoptera frugiperda*. We found that the Bayesian semi-parametric MRH models performed better at capturing the characteristics of the distribution associated with the

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The experiment described above gives rise to data of the form

$$\blacktriangle \; t_{ij}, \; c_{ij'}; \quad i = 1, \ldots, k; \quad j = 1, \ldots, 10,$$

where t_{ij} represents the time of death or time of censoring (within 12-h intervals) of the ith larva in the jth soybean genotypic group (with the artificial diet being treated as the 10th group). We have right censored mortality data for 122 larvae that survived the experiment. The censoring indicator, c_{ij} is a binary variable with 0 denoting right censoring (death not observed within the experimental time frame) and 1 otherwise

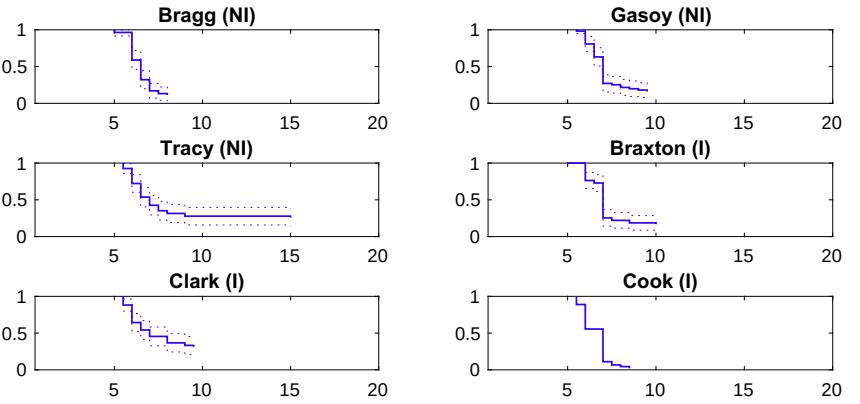

Bragg (NI)
Gasoy (NI)
Tracy (NI)
Braxton (I)
Clark (I)
Cook (I)
1
0.5
0
5
10
15
20

Table 1 Table of estimated Kaplan–Meier mean and median survival times (in days) for each genotype along with the respective sample sizes (Brookmeyer 2014)

Genotype	Median	Mean	Sample size
Williams	6 42	7 15	44
Stonewall	6 23	7 42	59
Gasoy	6 68	7 26	57
Bragg	6 17	7 01	56
Braxton	6 74	7 20	60
Clark	6 74	7 37	59
Davis	6 38	7 38	60
Tracy	6 67	7 41	54
Cook	6 13	6 62	45
Diet	–	9 49	60

The median survival time for the Diet group is not calculated because the diet survival function does not fall below 0.5 in our data set

To start, we consider distributions drawn from the extensive family of generalized gamma distributions such as Weibull, lognormal and gamma which are some of the most commonly used distributions for parametric modeling of time-to-event data (Cox et al 2007). Additionally, we look at various ways of building these parametric models

our data to capture a possible peak in hazard during our study period. The likelihood function for this model is given as:

$$\prod_{j=1}^{10}\prod_{i=1}^{n_j}\left[\frac{1}{\sigma_j\sqrt{2\pi}}\int_{t_{ij}-0.5}^{t_{ij}}\frac{1}{s}\exp\left[\frac{-\left(\log s-\mu_{j'}\right)^2}{2\sigma_j^2}\right]ds\right]^{c_{ij}}$$

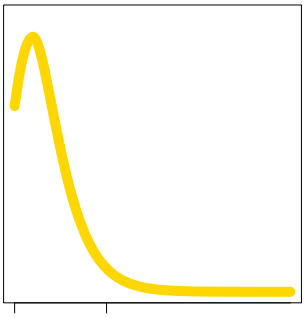
$$\frac{1}{2}$$

model is given as:

$$
\begin{aligned}
&\prod_{j=1}^{10} \frac{1}{j\sigma_a\sqrt{2\pi}} \exp\left(-\frac{\left(\log j' - a'\right)^2}{2\sigma_a^2}\right) \\
&\times \frac{1}{\sigma_j\sigma_b\sqrt{2\pi}} \exp\left(-\frac{\left(\log \sigma_{j'} - b'\right)^2}{2\sigma_b^2}\right) \\
&\times \prod_{i=1}^{n_j} \left(\frac{1}{\sigma_j\sqrt{2\pi}} \int_{t_{ij}-0.5}^{t_{ij}} \frac{1}{s} \exp\left(\frac{\left(\log s' - j'\right)^2}{2\sigma_j^2}\right) ds\right)^{c_{ij}} \\
&\times \left(\frac{1}{2} - \frac{1}{2}\mathrm{erf}\left(\frac{\log t_{ij'} - j}{\sqrt{2}\sigma_j}\right)\right)^{1-c_{ij}}
\end{aligned}
\tag{10}
$$

3.3.1 Ba e ia e i- a a e ic a al i

Here, we present a semi-parametric analysis in a Bayesian framework that estimates



covariates, so the log-likelihood for all N larvae is:

$$\log L(\boldsymbol{\beta}, \mathbf{H}, \mathbf{R}, \mathbf{X}) = \sum_{i=1}^{N} c_i \{\log h_0(T_{i'}) + X_i'\boldsymbol{\beta} - \exp(X_i'\boldsymbol{\beta}) H_0(T_{i'})\}, \quad (15)$$

where $H_0(T') = -\log S_0(T')$, is the cumulative baseline hazard. Here, X' represents the $N \times 10$ design matrix of 10 group indicator covariates. The columns are binary coded representing whether a larva, represented by a row, belongs to the ith group.

2. **N - a Ha a A**
The log-likelihood for all N larvae in $\mathcal{S}$ strata together is:

$$\log L(\boldsymbol{\beta}, \mathbf{H}, \mathbf{R}, \mathbf{X}) = \sum_{s=1}^{\mathcal{S}} \sum_{i=1}^{N_s} c_i \{\log h_{0,s}(T_{i,s'}) - H_{0,s}(T_{i,s'})\} \quad (16)$$

Here, we have 10 strata representing nine genotype and one diet group. In this model, we have no covariates so the design matrix and are no longer present in the likelihood function. Instead, we have the genotypes and diet being categorized as strata s with their own baseline hazards. Thus, each N_s represents the number of larvae in genotype s.

3. **N - a Ha a A G**

3.4 Model fitting

The parametric models were fitted using a custom maximum likelihood optimization code in MATLAB, based on Newton-Raphson algorithm with numerical first- and second-order derivatives. We specified the starting values based on the group sample statistics such as the mean and variance. The MRH models were estimated using the Bayesian framework and MCMC in the R package 'MRH' (Dukic and Dignam 2007; Bouman et al 2005; Hagar et al 2014; Chen et al 2014) where *M*

where p_{WAIC} is defined as the effective number of parameters,

$$p_{WAIC} = \sum_{i=1}^{n} \text{var}_{post}\left(\log p\left(y_i|\theta\right)\right) \tag{22}$$

Similarly, the log pointwise predictive density lppd in Eq. 21 is calculated as:

$$\text{computed lppd} = \sum_{i=1}^{n} \log\left(\frac{1}{M}\sum_{m=1}^{M} p\left(y_i|\theta^m\right)\right) \tag{23}$$

over M posterior draws and n data points. By comparing across all the information criteria, we hope to choose the best model that accounts for both the goodness of fit and the number of fitted parameters.

4 R

For each candidate model (Table 2), we estimated the model parameters using either maximum likelihood or Bayesian posterior mean estimates (under vague priors), and calculated each of the information criteria scores. For the BIC and AIC computation in MRH models we used the total number of parameters (including prior parameters which are estimated from the data), because it is the worst case scenario for the Bayesian MRH models, as it puts the maximum amount of penalty possible on them. This avoids the difficulty with counting the effective number of parameters in Bayesian hierarchical models (Spiegelhalter et al 2002), by giving an upper bound on the BIC and AIC for these models. For the random effect models, we presented a range for AIC and BIC, corresponding to the lowest penalty (counting only the likelihood-level parameters and not the random effect distribution parameters) and the highest penalty (counting all parameters, including those from the random effect distribution.)

In general, the Bayesian semi-parametric models had uniformly lower model selection criteria than any of the parametric models. The Bayesian models performed better under the worst penalty than the parametric models under the lowest penalty. Within

Table 2 Information criteria $\blacktriangle_{IC}$ (IC - min(IC)) calculated for each of the models used to fit the larval time to death data

Model (summary)	k	◀

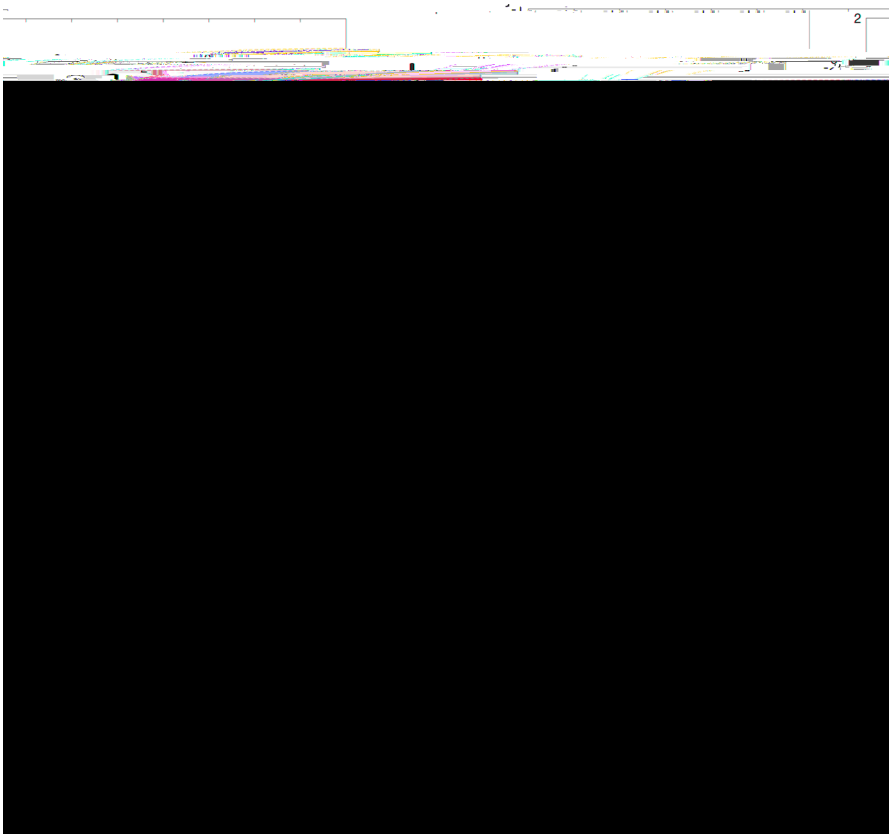
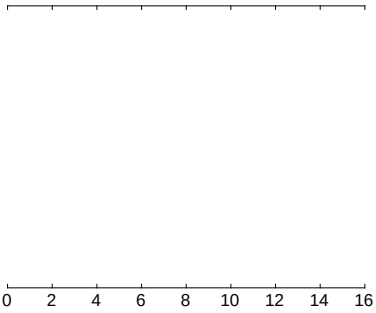


Fig. 3 Log hazard rates resulting from the maximum likelihood estimation of the individual parametric models for each genotype and diet. The shaded regions represents the 95% pointwise confidence interval associated with each estimate

models seem to have a difficult time capturing the decrease in the hazard function over time, although the lognormal model does better than the rest.

Figure 4 shows the estimated hazard functions for our clustered parametric models with lognormal distributions. The two cluster model in Fig. 4a shows a much higher hazard rate (approximately 5 times higher) associated with consuming infected soybean leaves compared to the diet group that did not consume soybean leaves. We see a similar hazard behavior in the three cluster model in Fig. 4b. Interestingly, the almost entirely overlapping hazard curves for the induced and non-induced genotypic groups imply that there is very little difference in hazard associated with the two groups except for a wider confidence band associated with the non-induced genotypes. However, as


0
2
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14
16

because while both the Weibull and gamma models are flexible and allow for hazard rates that are non-constant, they are constrained to have monotonic hazard shapes. Hence, they will fit any dataset with a non-monotonic hazard rate poorly. However, the lognormal distribution does allow for non-monotonic shapes of hazard function (e.g., inverse bath-tub shaped) but still fails to capture the decrease in the hazard function rapidly enough due to the strong smoothness property. These approaches simply fail to maximize the information drawn from the mortality data in this case. Hence, our results demonstrate the pitfalls of assuming a commonly used parametric form for the mortality time for computational and analytic simplicity without further analysis of the hazard's shape. The apparent decrease in hazard modeled by all the MRH models suggests that the probability of dying for the larvae decreases dramatically after the hazard has peaked around day 7.5 of the infection. Biologically, this fits well with the fact that if the larvae are able to survive the infection up until a certain time point, they should be expected to survive well beyond that time point as well.

Figure 7 shows the estimated survival curves for different genotypes based on our semi-parametric MRH approach (where the baseline hazard is jointly estimated along with the covariate effects), and based on the Cox proportional hazard model (where the Breslow estimator (Breslow 1972) is used to estimate the baseline cumulative hazard). The Breslow estimator is a non-parametric maximum likelihood estimator for the cumulative baseline hazard estimate, and is based, in part, on the Cox partial likelihood covariate effect estimates. While the performance of this combination of non-parametric likelihood and partial likelihood estimators in finite samples is not entirely understood, it has been observed that it can lead to non negligible bias and underestimated uncertainty for the hazard function (Hagar and Dukic 2015). On the other hand, the Bayesian MRH model is explicitly formulated to estimate the joint finite-sample uncertainty through the joint posterior distribution, which is based on the joint likelihood for the hazard function and covariate effects. Hagar and Dukic (2015) present an extensive comparison of the performance of the MRH model with other commonly used, comparable semi-parametric survival models including the Cox model. They found that the Cox model based estimators for the baseline hazard function did not perform well in terms of bias and mean square error, unlike the MRH. Therefore, if accurate hazard shapes and a proper quantification of the associated uncertainty are of interest, including the option of relaxing the proportional hazard assumption, the MRH model is a valuable option.

Our results also show that there is clearly a larger hazard associated with consuming the virus with a soybean leaf compared to consuming the virus without ingesting leaf tissue. Our best-supported model treats the diet as the baseline and characterizes the hazards of each genotype as a proportion of this baseline. Thus, studying the covariate effect of the different genotypes helps us understand the risks or benefits associated with the fall armyworm food quality and its effect on the speed of kill. Given that the infection process in the field involves a tritrophic interaction that includes the host's food resources, our results show that ignoring the effect of the resource could be costly. Clearly, the data demonstrate that different soybean genotypes play a role in the time to death for the host. There has been extensive work done on host and pathogen variability and genetic diversity as a way of understanding host-pathogen interactions (Elderd et al 2008; Myers and Cory 2016; Kennedy et al 2014; Dwyer

et al 1997). However, the impact of plant genetic diversity on within host processes has not been studied or modeled extensively (but see Shikano et al 2017). Our results strongly suggest that any kind of within-host interaction model for the fall armyworm should include plant genotypic variability. The importance of the resources consumed by a host in helping or hindering individuals fighting off an infection should not be limited to just the interactions considered here (Lively et al 2014). The next step would be to move beyond the within-host effects and incorporate our findings in a model examining the population-level consequences of this tritrophic interaction that includes a plant/resource genotype component.

Lastly, these methods are applicable to any kind of non-death event data in ecology and evolution where hazard (albeit interpreted differently) is of primary interest, and show that flexibility of a semi-parametric approach can allow researchers to maximize the amount of information drawn from their data.

Ack ledge e We thank the Elderd Lab at Louisiana State University for their help and guidance

Integrating both sides from 0 to t,

$$\int_0^t h(y')dy = \int_0^t \frac{f(y')}{1-F(y')}dy$$
$$H(t') = -\ln(1-F(t')) \quad [\text{Since, } F'(t') = f(t')]$$
$$H(t') = -\ln(S(t'))$$
$$\exp(-H(t')) = S(t')$$

A 2: A L -

– The corresponding log-likelihood function for Eq. 4,

$$\sum_{j=1}^{n_j}\sum_{i=1}^{n_j} c_{ij}\left[\log k_{j'} - k_j \log \theta_{j'} + \log \int_{t_{ij}-0.5}^{t_{ij}} s^{k_j-1}\exp\left(\frac{-s}{\theta_j}\right)^{k_j} ds\right] + (1-c_{ij'})\left(\frac{t_{ij}}{\theta_j}\right)^{k_j} \tag{26}$$

– The corresponding log-likelihood function for Eq. 5,

$$\sum_{j=1}^{n_j}\sum_{i=1}^{n_j} c_{ij}\log\left[\gamma\left(\frac{t_{ij}}{\theta_{j'}}\right)^{k_j} - \gamma\left(\frac{t_{ij}-0.5}{\theta_j}\right)^{k_j}\right] + (1-c_{ij'})\log\left[1-\gamma\left(\frac{t_{ij}}{\theta_{j'}}\right)^{k_j}\right] \tag{27}$$

– The corresponding log-likelihood function for Eq. 6,

$$\sum_{j=1}^{n_j}\sum_{i=1}^{n_j} c_{ij}\log\left[\frac{1}{2}\mathrm{erf}\left(\frac{\log t_{ij'} - \mu_j}{\sqrt{2}\sigma_j}\right) - \frac{1}{2}\mathrm{erf}\left(\frac{\log t_{ij}-0.5' - \mu_j}{\sqrt{2}\sigma_j}\right)\right] + (1-c_{ij'})\log\left[\frac{1}{2} - \frac{1}{2}\mathrm{erf}\left(\frac{\log t_{ij'} - \mu_j}{\sqrt{2}\sigma_j}\right)\right] \tag{28}$$

– The corresponding log-likelihood function for Eq. 9,

$$\begin{aligned}
&\sum_{j=1}^{10} \Big[\left(k_a - 1\right) \log k_j - \frac{k_j}{\theta_a} - \log \Gamma\left(k_a\right) - k_a \log \theta_a + \left(k_b - 1\right) \log \theta_j \\
&- \frac{\theta_j}{\theta_b} - \log \Gamma\left(k_b\right) - k_b \log \theta_b \\
&+ \sum_{i=1}^{n_j} c_{ij} \log \left[\gamma\left(\frac{t_{ij}}{\theta_j}, k_j\right) - \gamma\left(\frac{t_{ij} - 0.5}{\theta_j}, k_j\right) \right] \\
&+ \left(1 - c_{ij}\right) \log \left[1 - \gamma\left(\frac{t_{ij}}{\theta_j}, k_j\right) \right]
\end{aligned} \tag{29}$$

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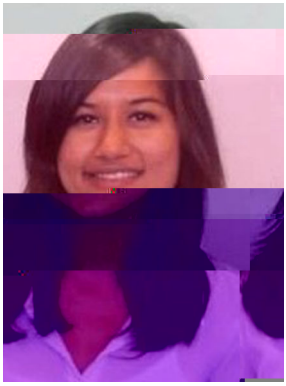

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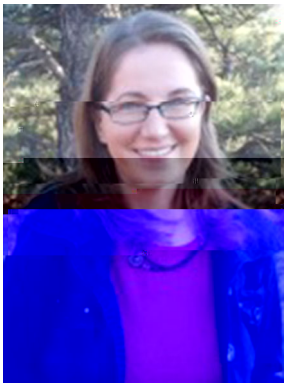

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