Multiple blood-feeding modeling study

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Introduction

Mosquito-borne diseases are a big problem.

Multiple blood-feeding, in its many forms, is a phenomenon that may multiply the transmission of mosquito-borne parasites.

Mechanisms and processes of mosquito blood-feeding

Descriptions and diagrams

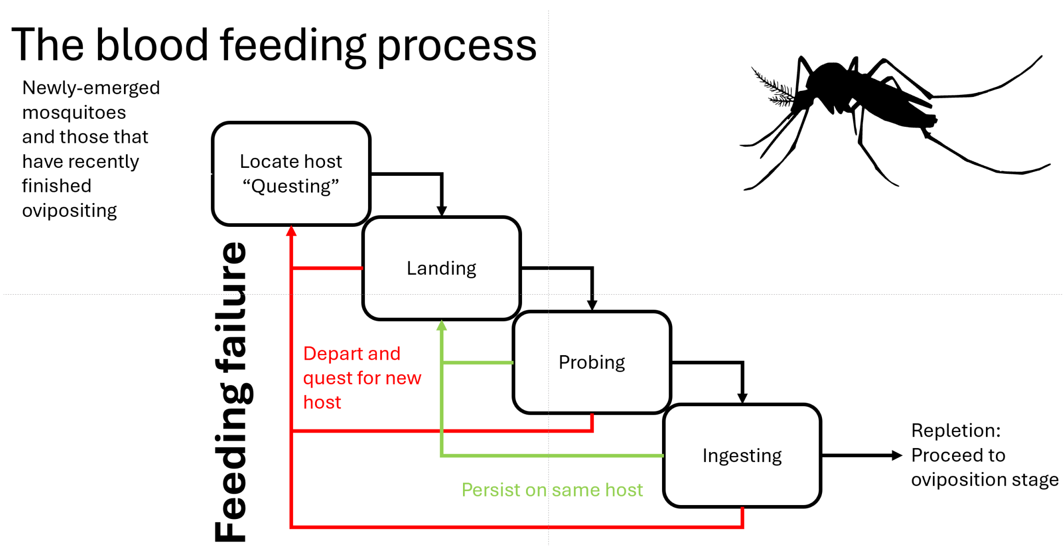


Figure 1: Cartoon of the mosquito blood-feeding process.

Methods

Box: Modeling processes with phase-type distributions

Model formulation

Parameterization

We assume the following parameter values for the biting parameters

Symbol	Description	Value
p_L	Probability of progressing from landing to probing	0.70
λ_L	Exit rate from landing stage (per minute)	0.10
p_P	Probability of progressing from probing to ingesting	0.80
λ_P	Exit rate from probing stage (per minute)	0.20
p_G	Probability of progressing from ingesting to ovipositing	0.90
λ_G	Exit rate from ingestion stage (per minute)	1.00
f	Probability of seeking a new vertebrate host given feeding failure	0.66

and the following for the remaining model parameters

Symbol	Description	Value
η	Extrinsic incubation rate	0e+00
μ	Mosquito mortality rate	0e+00
γ	Return to blood-feeding rate	0e+00
γ_H	Host recovery rate	0e+00
μ_H	Host mortality rate	0e+00
K_H	Host carrying capacity	1e+07
K_L	Larval mosquito carrying capacity	3e+02
ρ_L	Larval mosquito maturation rate	0e+00
μ_L	Larval mosquito mortality rate	0e+00
φ	Eggs per female per day	0e+00
β_P	Probing transmission probability	1e+00
β_G	Ingestion transmission probability	1e+00
β_H	To-host transmission probability	1e+00
β_V	To-mosquito transmission probability	1e+00
λ_Q	Questing rate	0e+00

Simulation

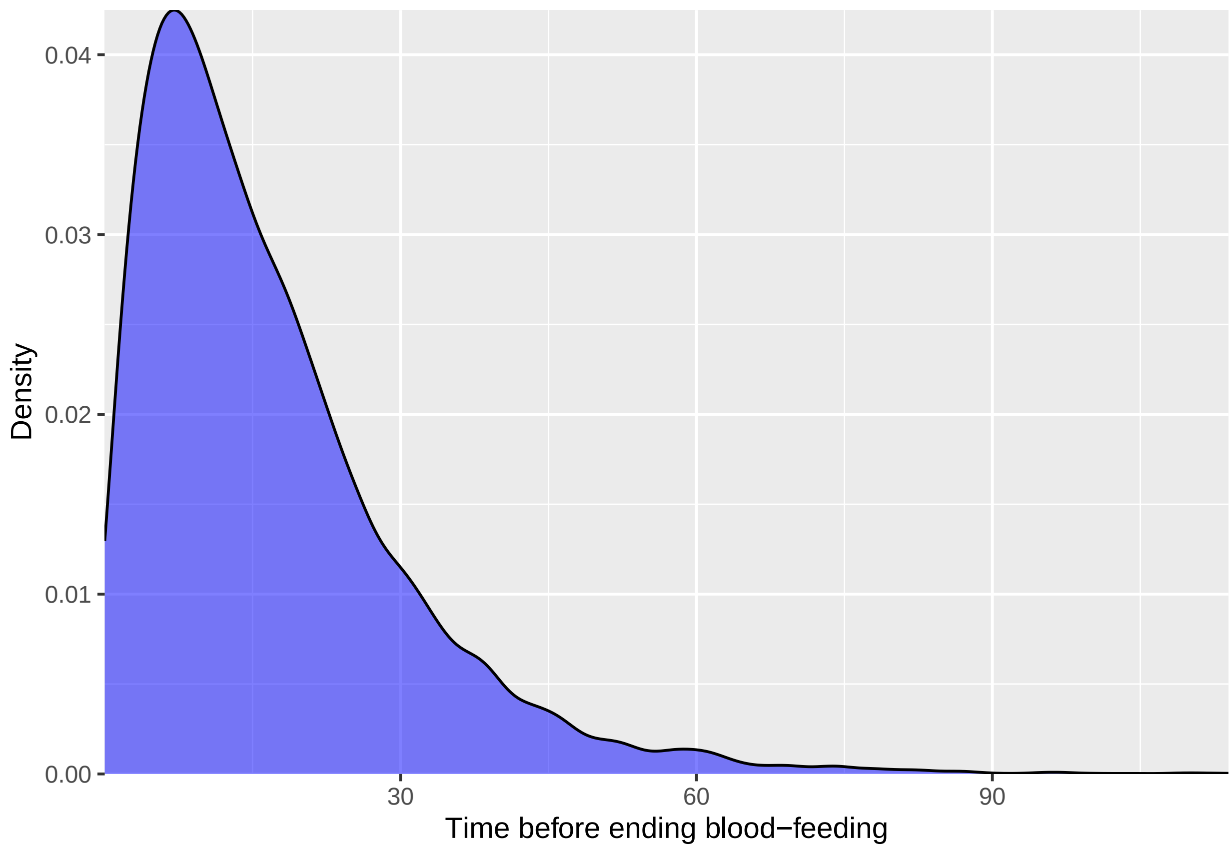
We simulate a set of measurements of the time it takes for a single mosquito seeking a blood meal on a specific host to no longer seek a blood meal. This data is heavily censored: we don't have information on whether the mosquito successfully completed a blood meal or if it was disrupted at any point in the feeding process. This simulation does not take into account the time that the mosquito spends questing, that is, we assume it has already located a suitable host to feed upon.

These parameters lead to a phase-type distributed waiting time for blood-feeding parameterized by the sub-intensity matrix A given by

$$A = \begin{bmatrix} -\lambda_L + (1-f)(1-p_L)\lambda_L & p_L\lambda_L & 0 \\ (1-f)(1-p_P)\lambda_P & -\lambda_P & p_p\lambda_P \\ (1-f)(1-p_G)\lambda_G & 0 & -\lambda_G \end{bmatrix} = \begin{bmatrix} -0.0898 & 0.07 & 0 \\ 0.0136 & -0.2 & 0.16 \\ 0.034 & 0 & -1 \end{bmatrix}$$

and initial vector $\alpha = (1, 0, 0)$.

This distribution takes the following approximate shape and has a mean of 16.8353168 minutes and standard deviation of 13.5063023 minutes. The 5% and 95% quantiles are at 2.0691565 minutes and 42.9387666 minutes, respectively.



We will use this simulated data set as a proxy for real data that might be collected to study the effects of multiple blood-feeding on transmission.

Results: Equilibrium analysis

Basic reproduction number

Existence and stability of equilibria

Results: Sensitivity analysis

Relationships among reproduction numbers and blood-feeding parameters

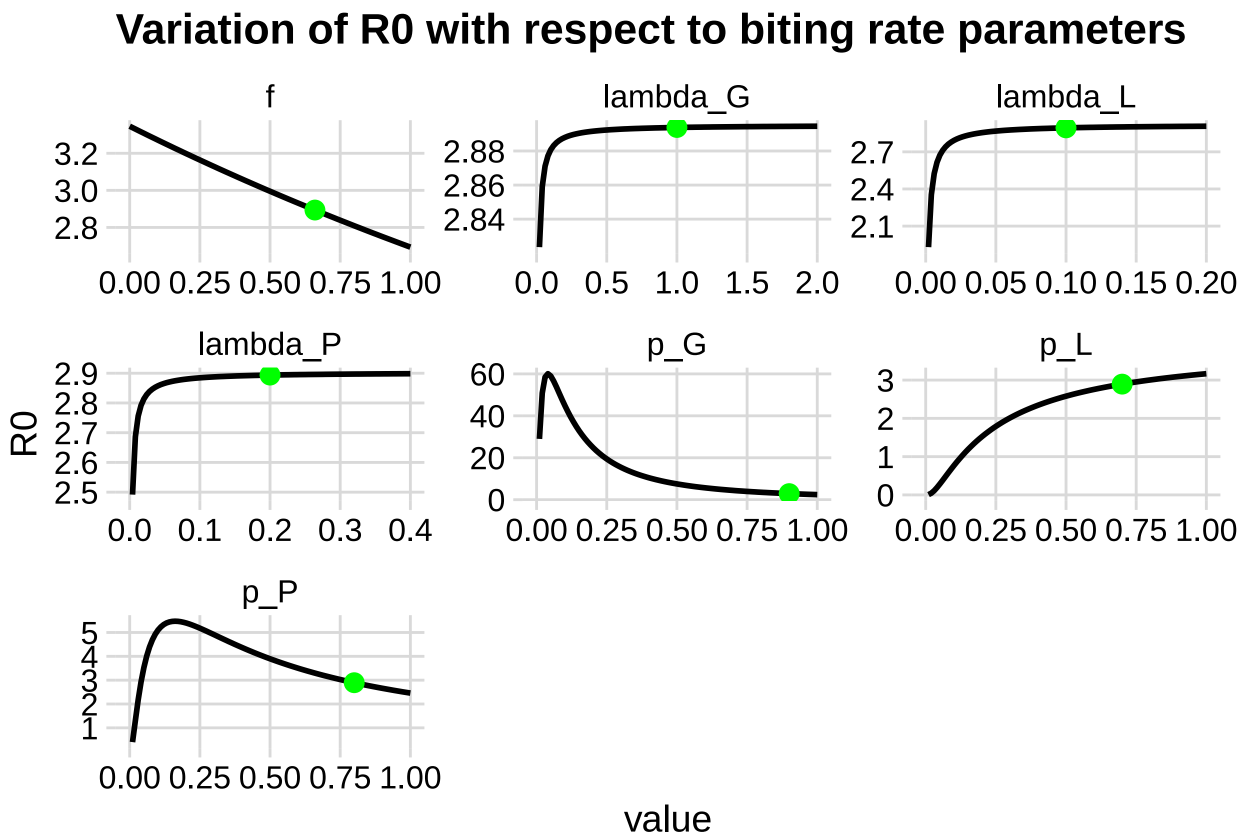


Figure 2: The basic reproduction and reproductive numbers as functions of the biting rate parameters. In each figure, only the labeled parameter is being varied. All other parameters are as in Tables 1 and 2.

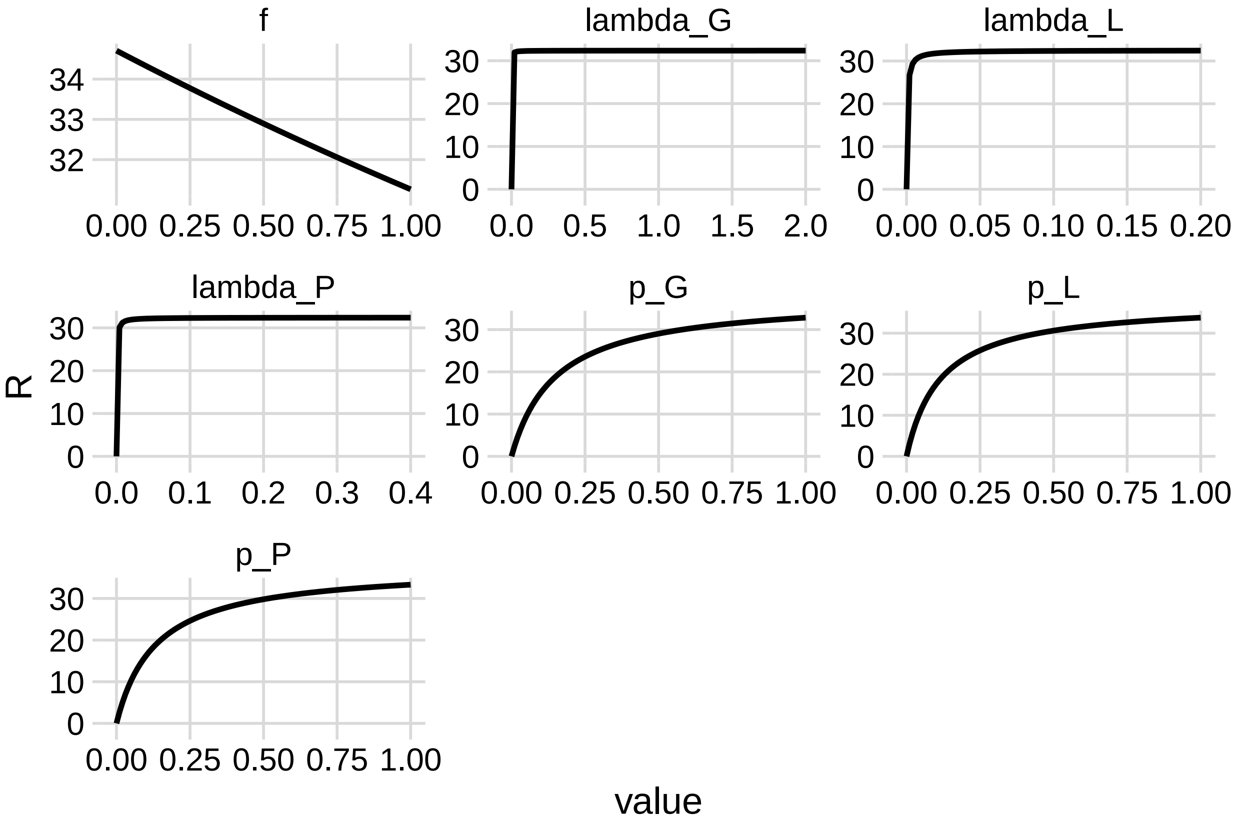


Figure 3: The basic reproduction and reproductive numbers as functions of the biting rate parameters. In each figure, only the labeled parameter is being varied. All other parameters are as in Tables 1 and 2.

PRCCs of R0 or R and blood-feeding parameters

Table of values

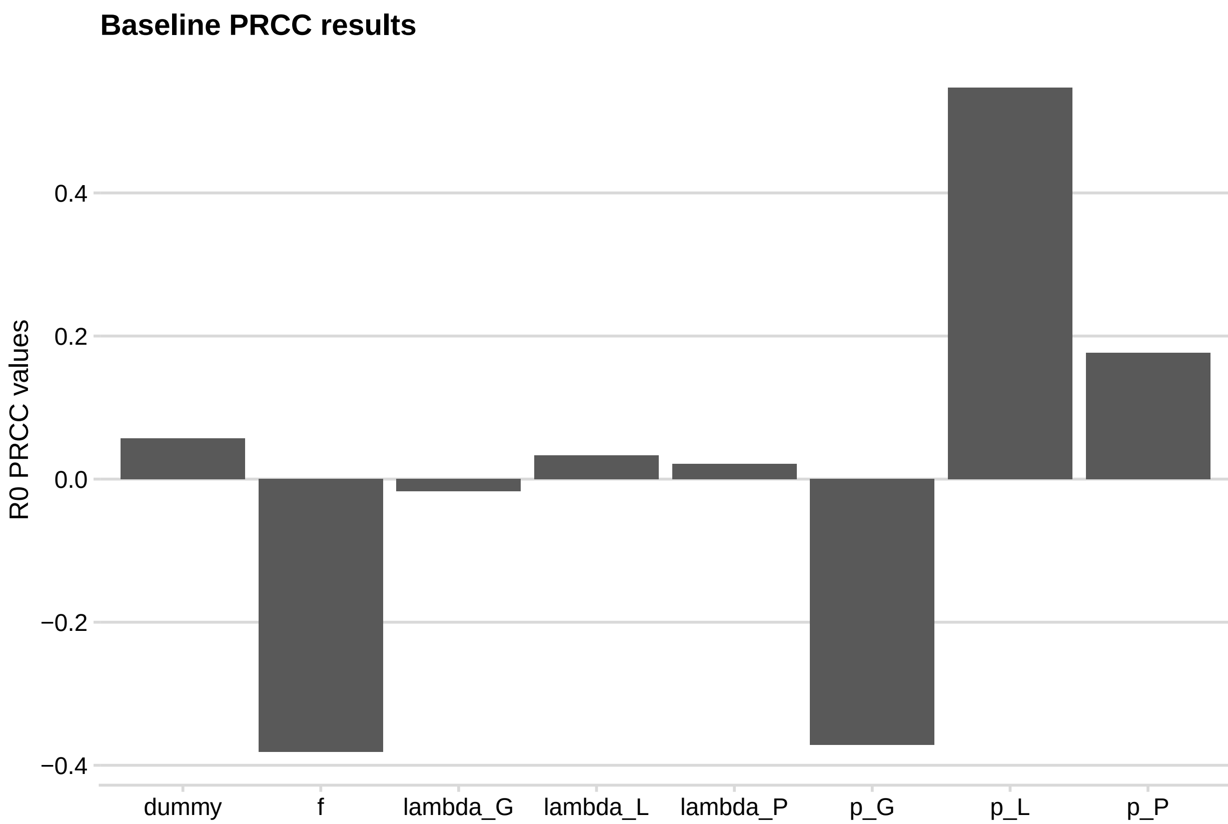


Figure 4: Table 3: Baseline PRCC values

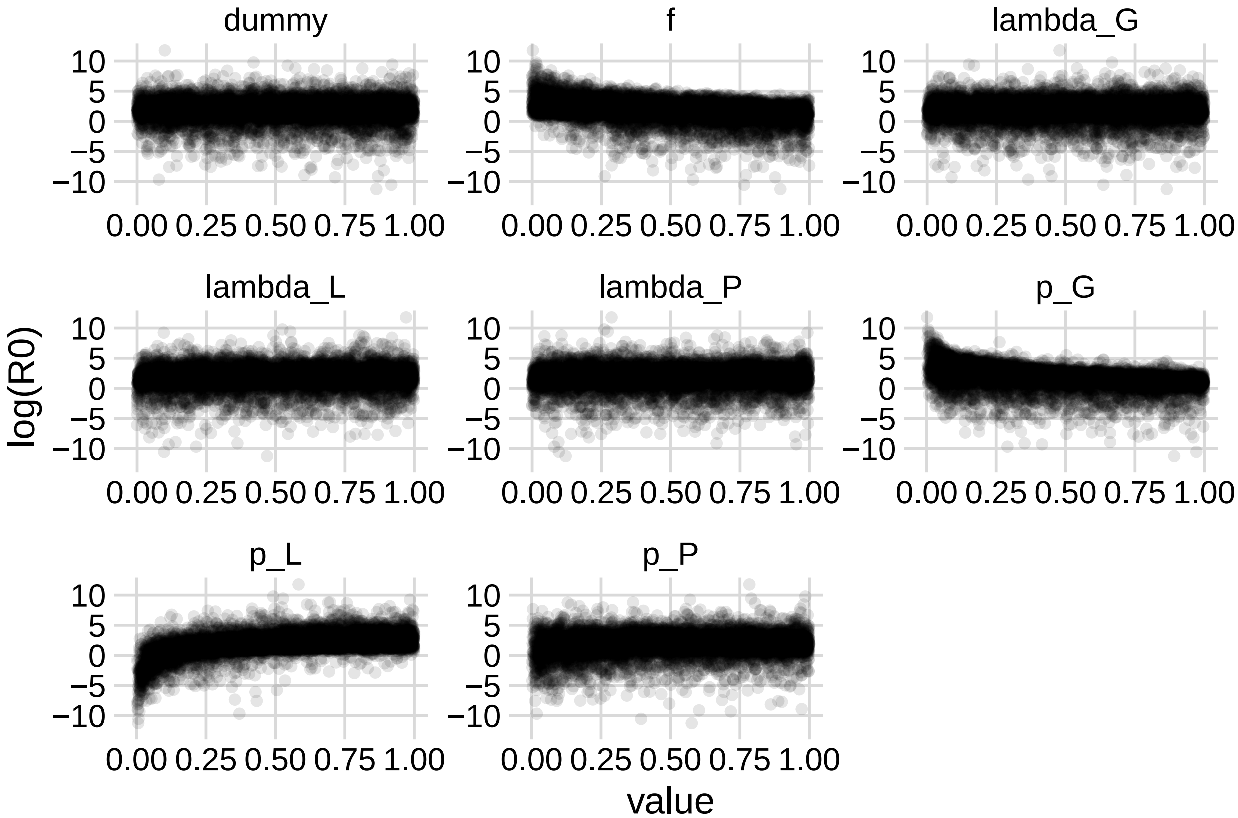


Figure 5: Test for the monotonicity of R0 with respect to Latin hypercube sampled blood-feeding parameters.

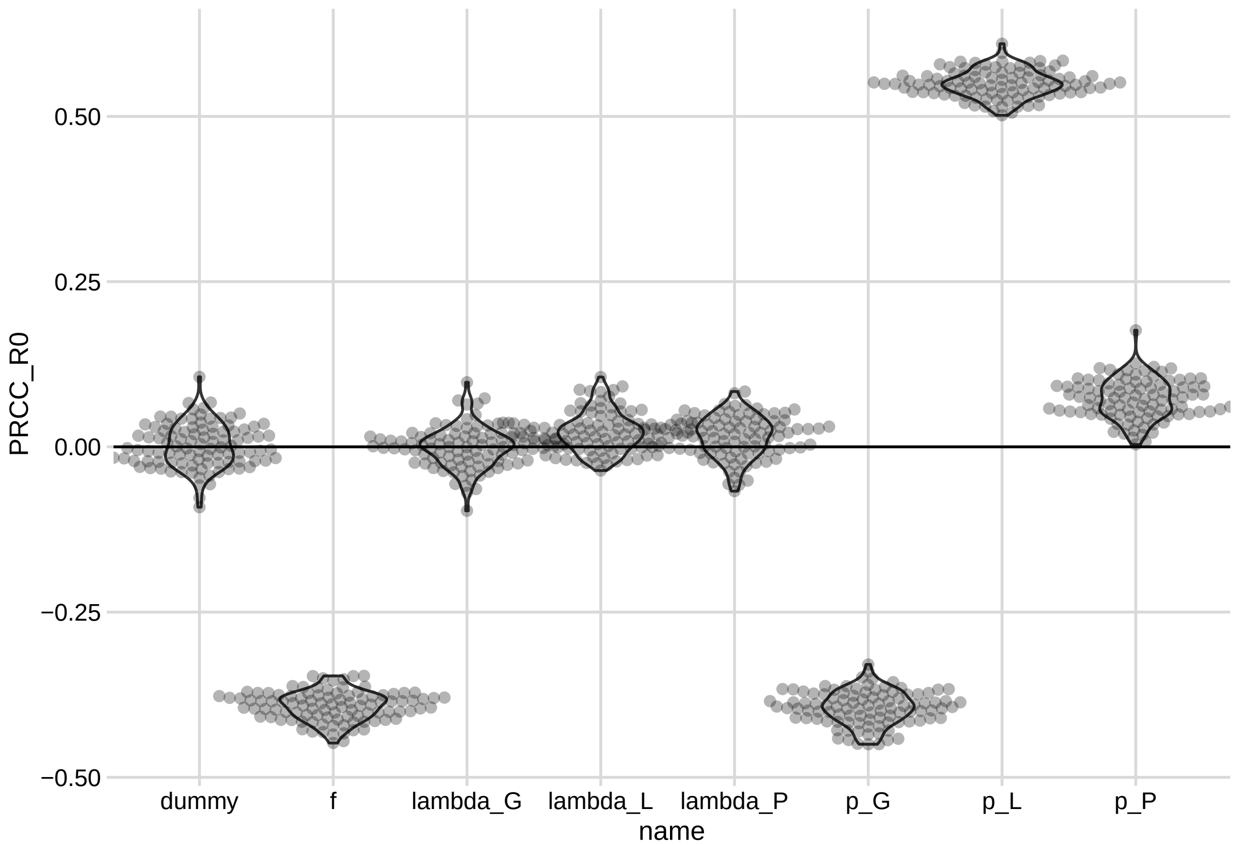
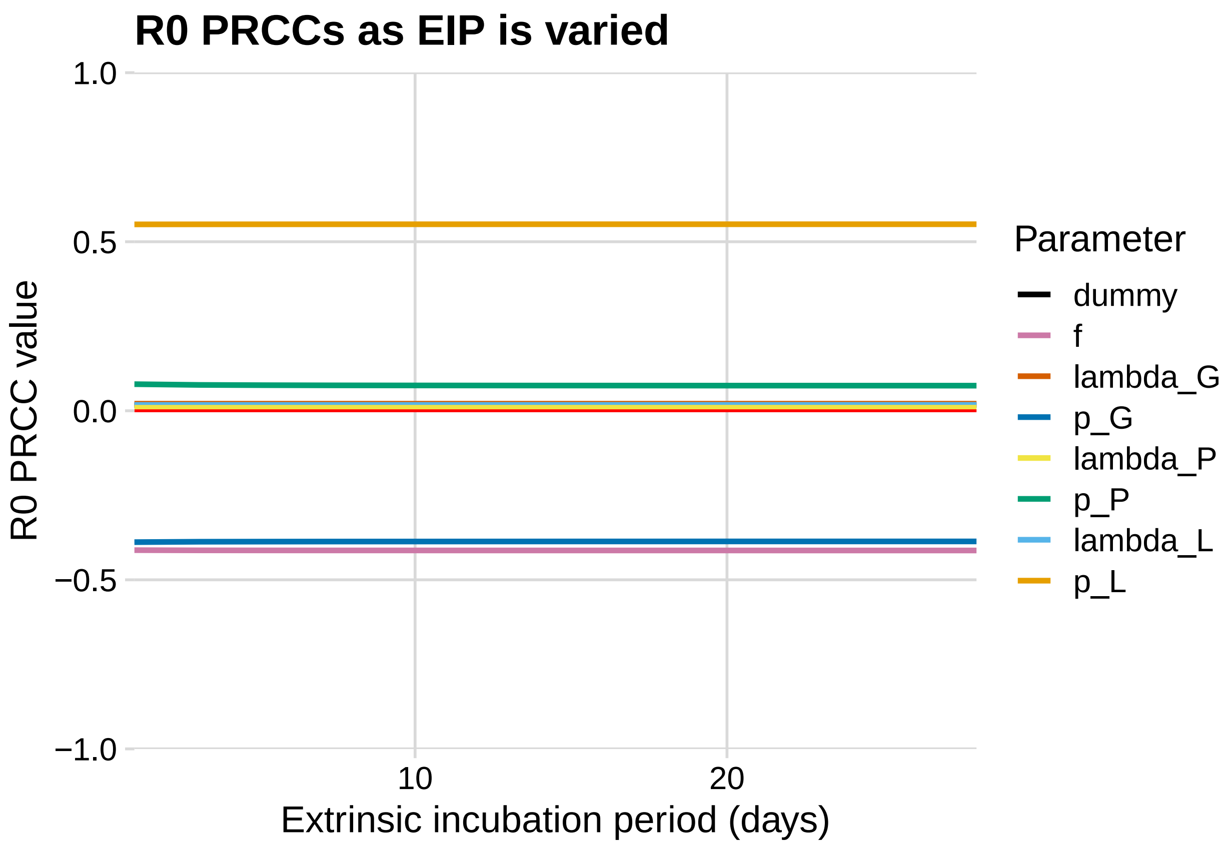
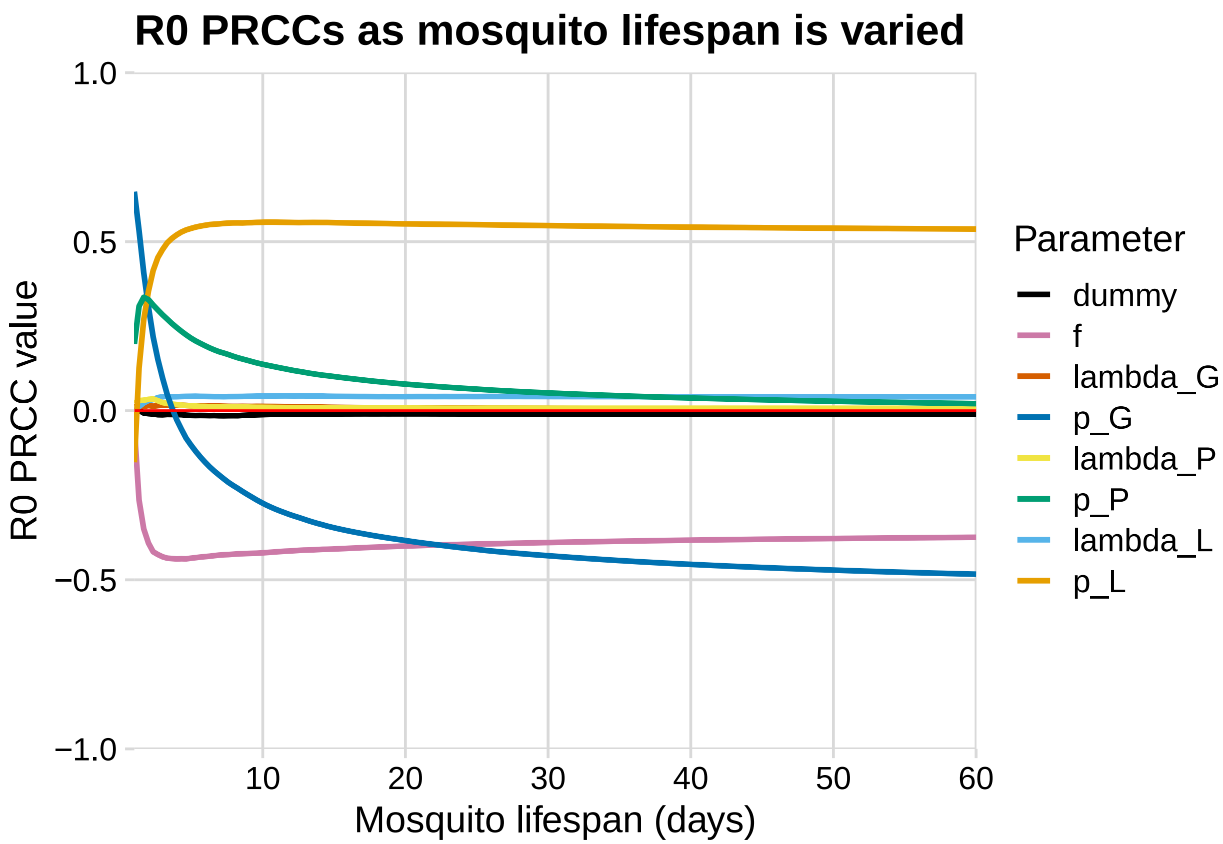


Figure 6: Diagnostic test of the variation in PRCC values using 10 independent calculations

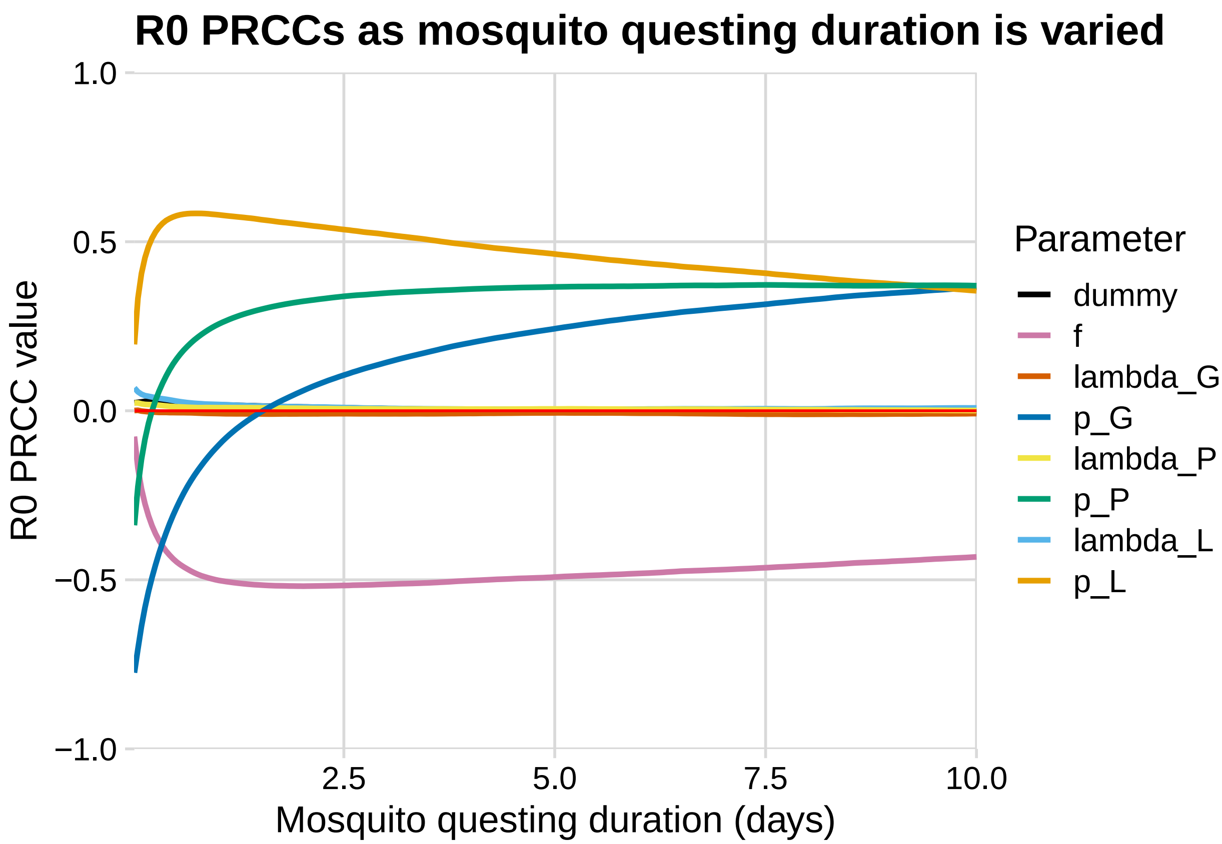
The global sensitivity of R_0 to the biting rate parameters does not change when the extrinsic incubation period is increased.



Similarly, changing the lifespan of the mosquito also does not impact the global sensitivity of R_0 to the biting rate parameters.



Let's see what happens when we increase the questing time



Results: Uncertainty analysis

Fitting phase-type distributions

We first need to estimate the parameters of the model from the available data. Because we are not certain of appropriate way to model the processes of multiple blood-feeding, we consider three types of models: empirical, phenomenological, and mechanistic. For the empirical model, we don't assume to know the actual underlying processes, essentially considering them a black box. We will consider three orders for this model: 1 (corresponding to an exponential distribution), 3 (for comparison with the mechanistic model), and 5. The phenomenological model focuses are getting the phenomenon right: that there is some disruption causing mosquitoes to take multiple blood meals. For now, we consider model orders of 3, 4, and 5. Finally, the mechanistic model incorporates what we know about the elements of the mosquito blood-feeding processes to directly estimate the parameters. These parameters align in definition with those used to simulate the test data.

For each model class, we use an expectation-maximization algorithm that uses Markov-chain Monte Carlo sampling to perform Bayesian inference on the parameter values. This means that we obtain posterior distributions for each of the parameters (or equivalently the matrix elements of A).

Empirical model

We can compare the waiting time distributions derived from these models with our simulated data.

Mechanistic model

Now considering the mechanistic model. We will make direct comparisons between this model, the simulated data, and the empirical model. First, we look at how the waiting time statistics compare.

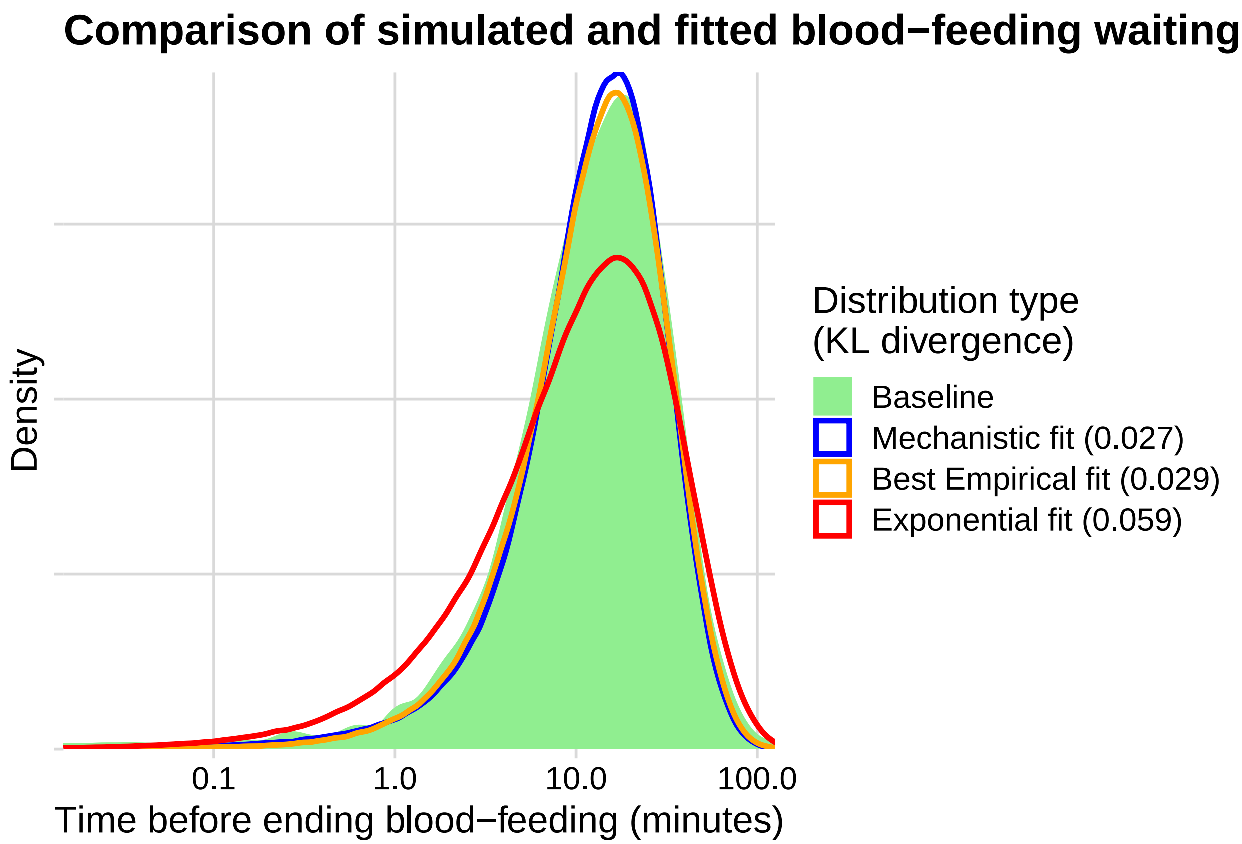


Figure 7: Comparison of approximated waiting-times for the original simulated data and fitted exponential, empirical phase-type, and mechanistic phase-type distributions.

Distributions of the mechanistic parameters compared to the those used in the simulations.

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## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
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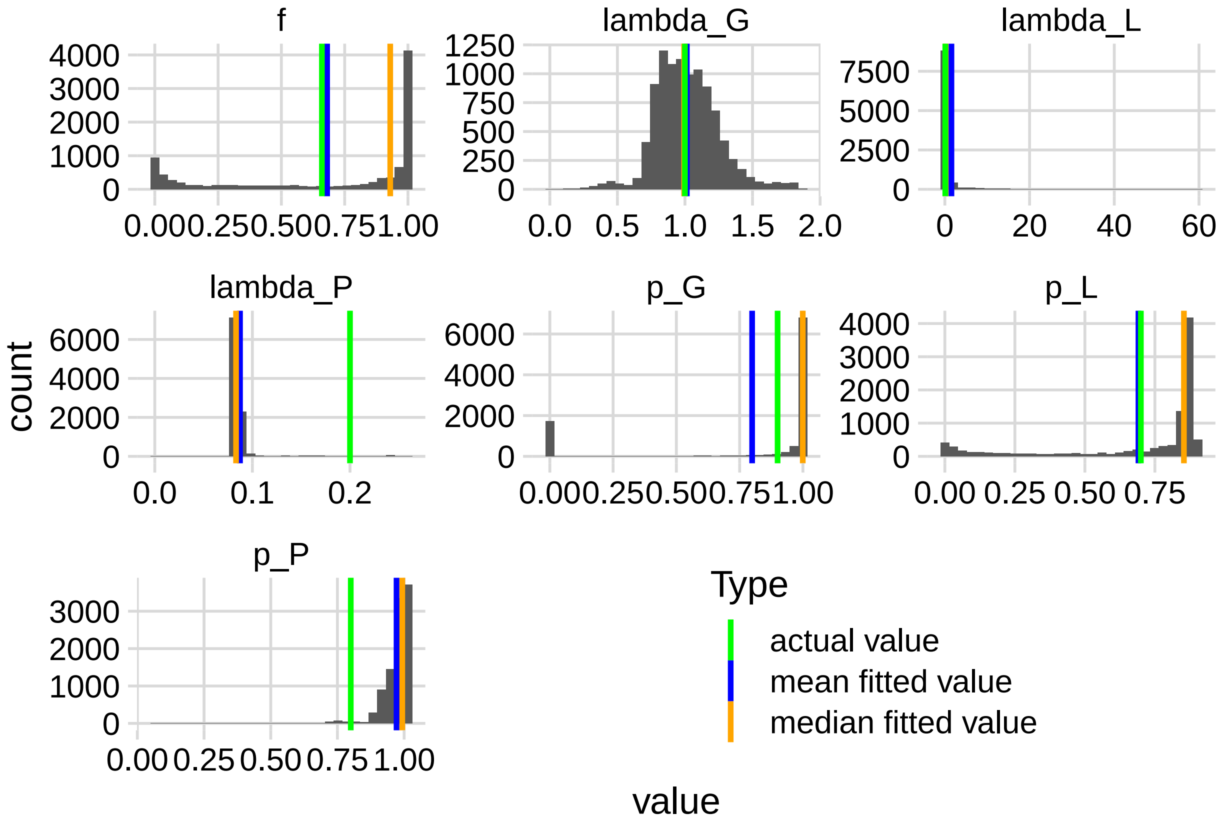
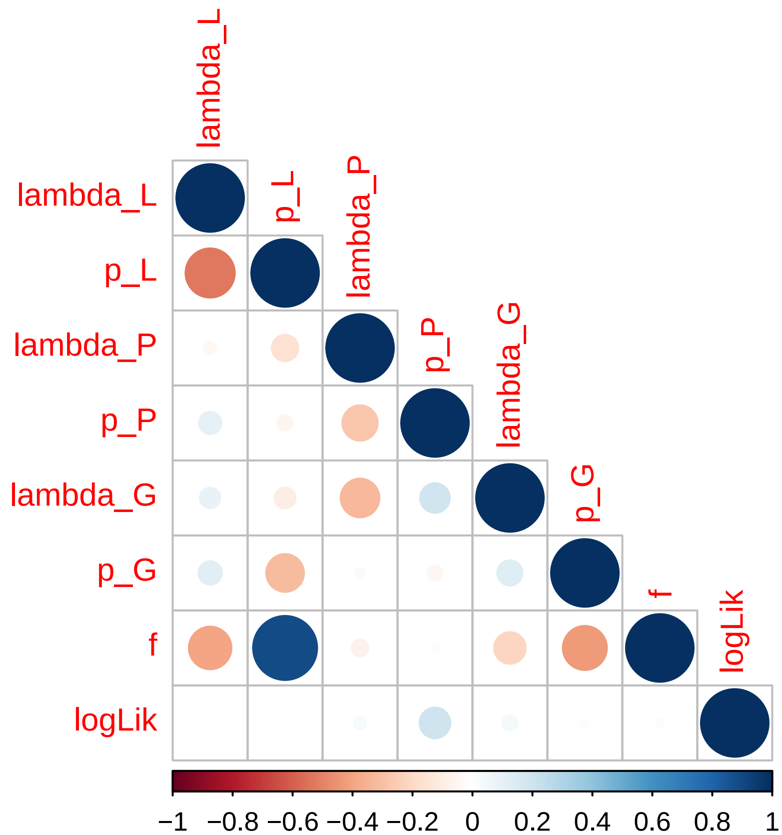
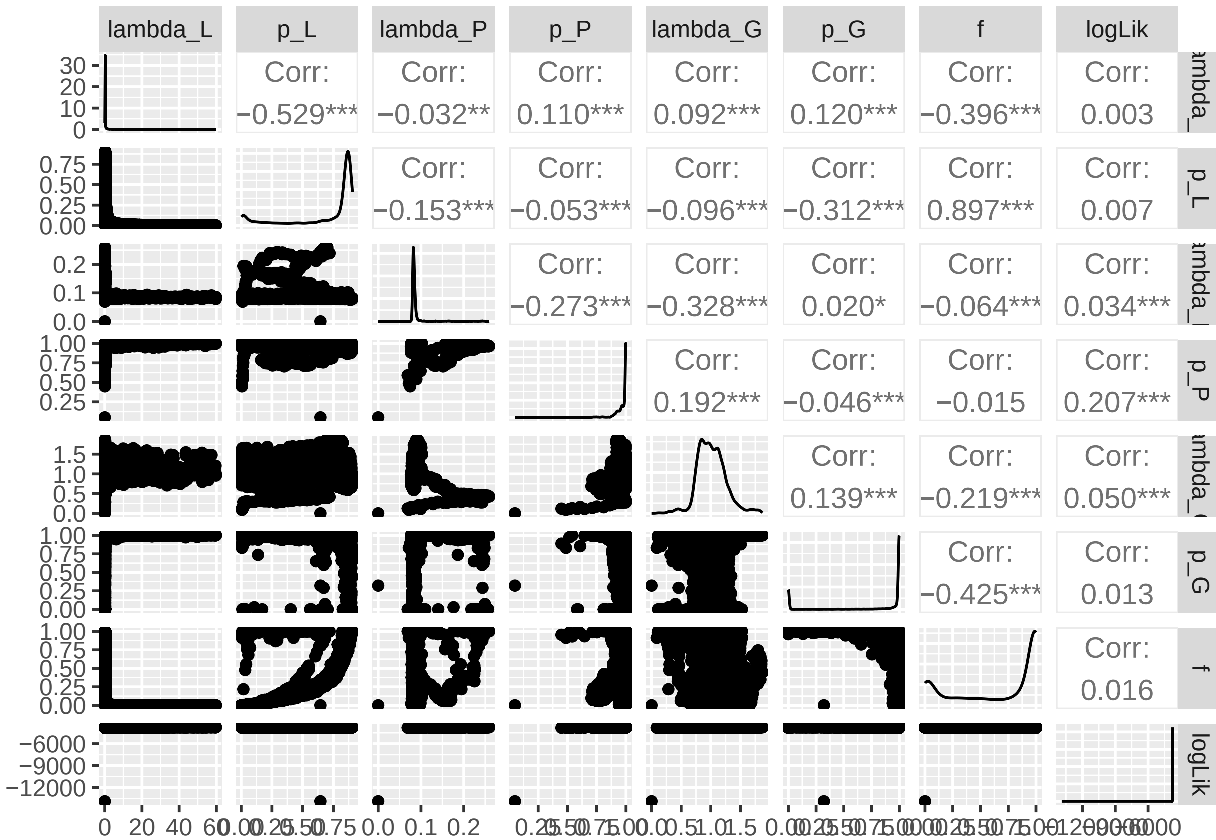


Correlations among the fitted parameters of the mechanistic model



Scatter plots showing associations among mechanistic parameters



Estimates of R0 from fitted parameter sets

Here we study how the blood-feeding parameters affect transmission via the basic reproduction number.

Discussion