Multiple blood-feeding modeling study

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Sensitivity analysis of the base model

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	1.1570e-04
μ	Mosquito mortality rate	3.3100e-05
γ	Return to blood-feeding rate	2.3150e-04
γ_H	Host recovery rate	9.9200e-05
μ_H	Host mortality rate	0.0000e+00
K_H	Host carrying capacity	1.0000e+07
K_L	Larval mosquito carrying capacity	3.0000e+02
ρ_L	Larval mosquito maturation rate	5.7900e-05
μ_L	Larval mosquito mortality rate	3.4700e-05
φ	Eggs per female per day	2.0833e-03
β_P	Probing transmission probability	1.0000e+00
β_G	Ingestion transmission probability	1.0000e+00
β_H	To-host transmission probability	1.0000e+00
β_V	To-mosquito transmission probability	1.0000e+00
λ_Q	Questing rate	2.0833e-03

Parameter estimation

Simulated data set

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

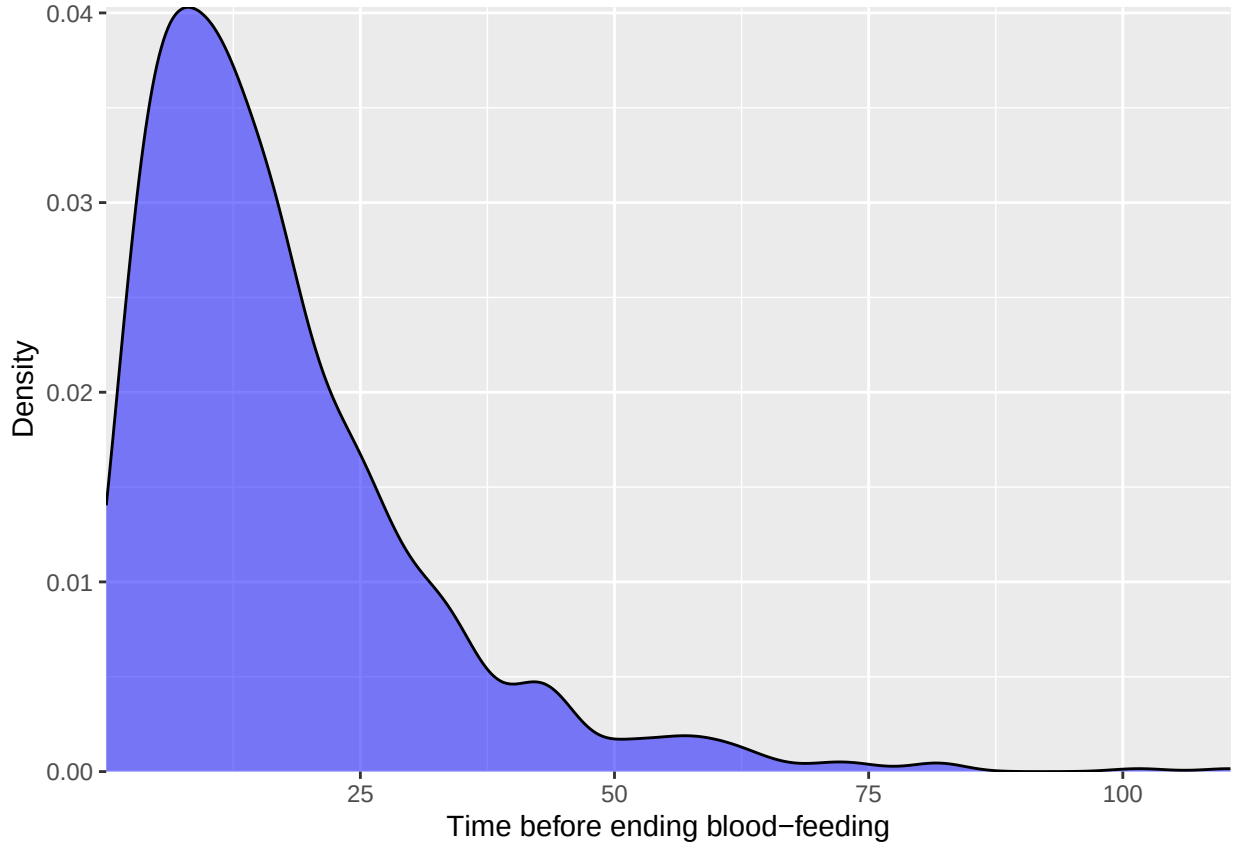
process. This simulation does not take into account the time that the mosquito spends questing, that is, we assume it has already located a suitable host to feed upon.

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 17.0784746 minutes and standard deviation of 14.0151679 minutes. The 5% and 95% quantiles are at 2.1875221 minutes and 43.9577527 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.

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

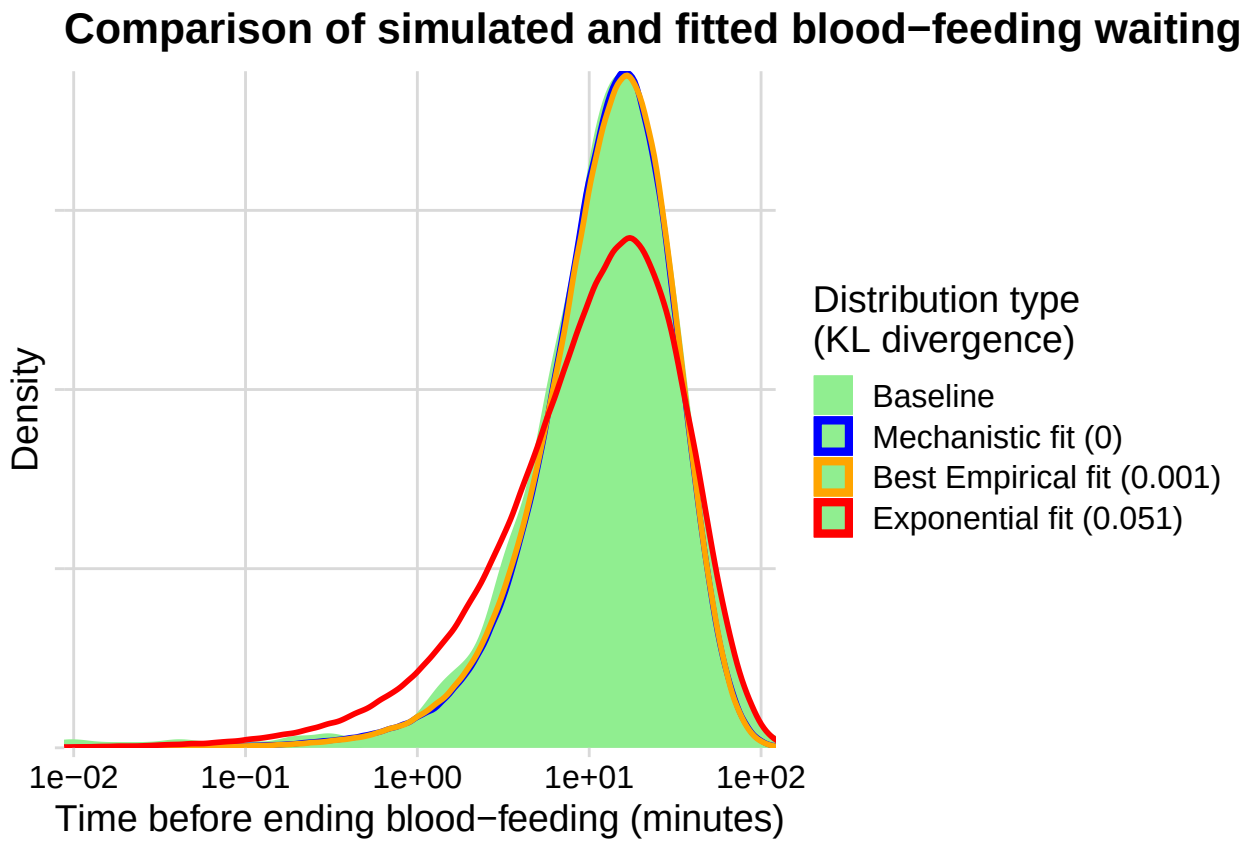
```
## Rows: 35000 Columns: 6
## -- Column specification --------------------------------------------------------
## Delimiter: ","
## dbl (6): iterate, order, row_index, col_index, value, logLik
##
## i Use `spec()` to retrieve the full column specification for this data.
## i Specify the column types or set `show_col_types = FALSE` to quiet this message.
```

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.

```
## Rows: 1000 Columns: 9
## -- Column specification --------------------------------------------------------
## Delimiter: ","
## dbl (9): iterate, lambda_L, p_L, lambda_P, p_P, lambda_G, p_G, f, logLik
##
## i Use `spec()` to retrieve the full column specification for this data.
## i Specify the column types or set `show_col_types = FALSE` to quiet this message.
```



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

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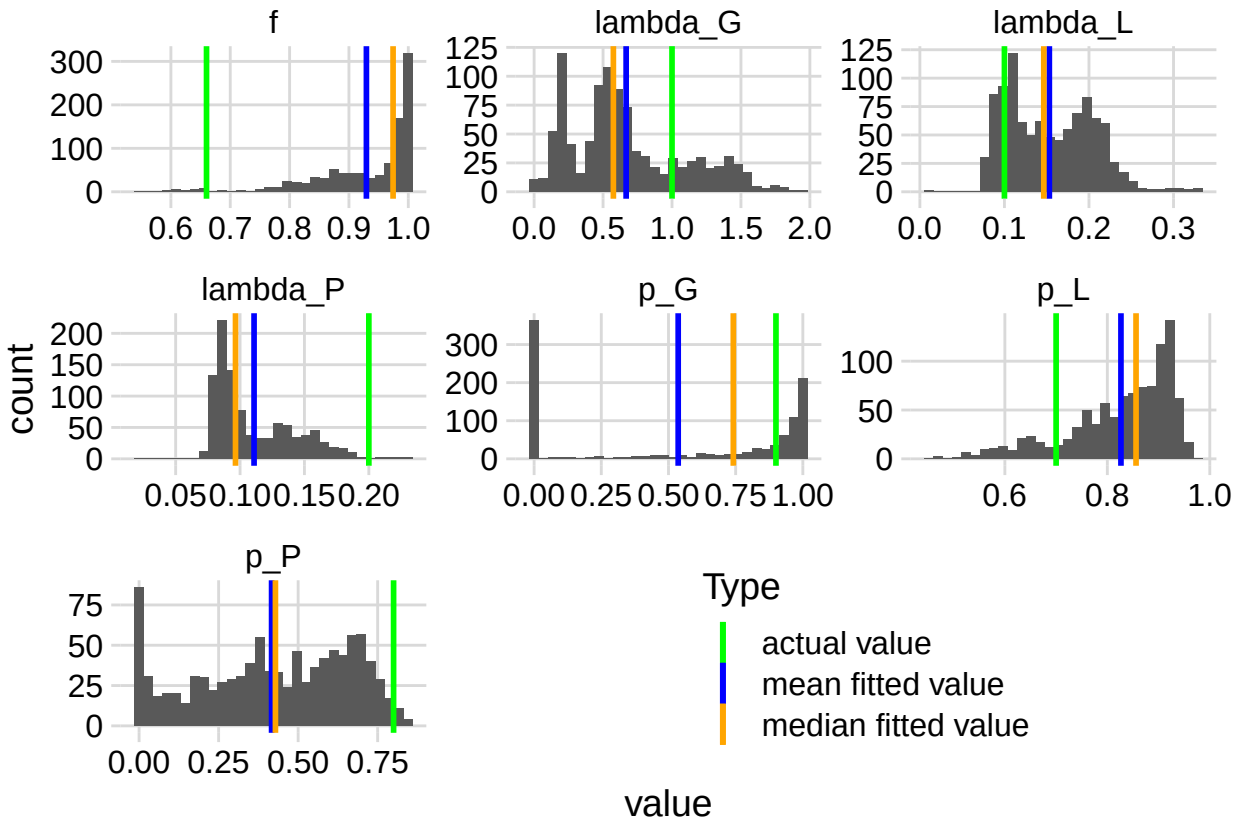
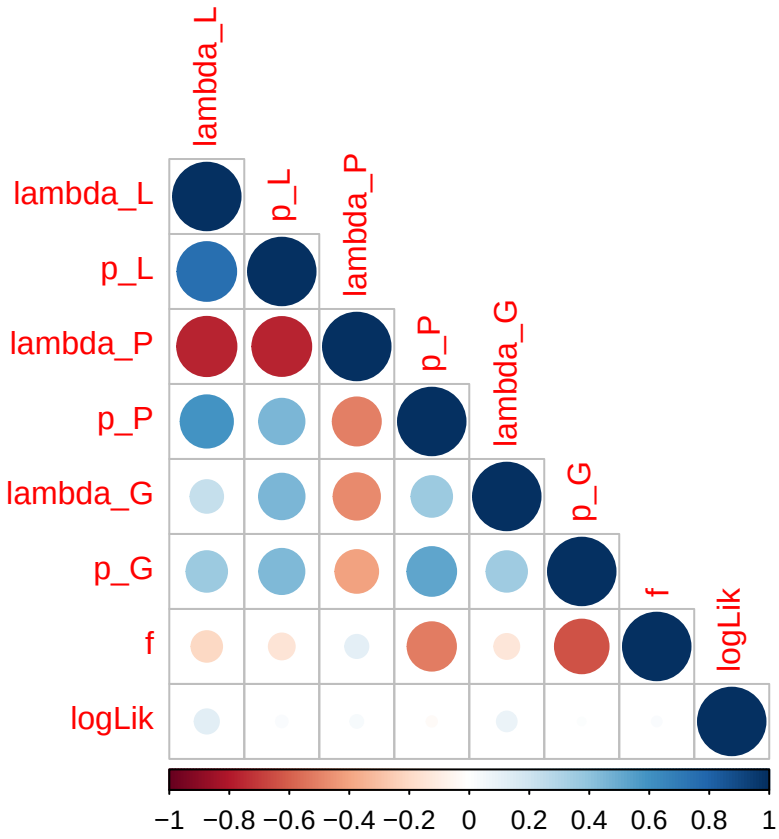
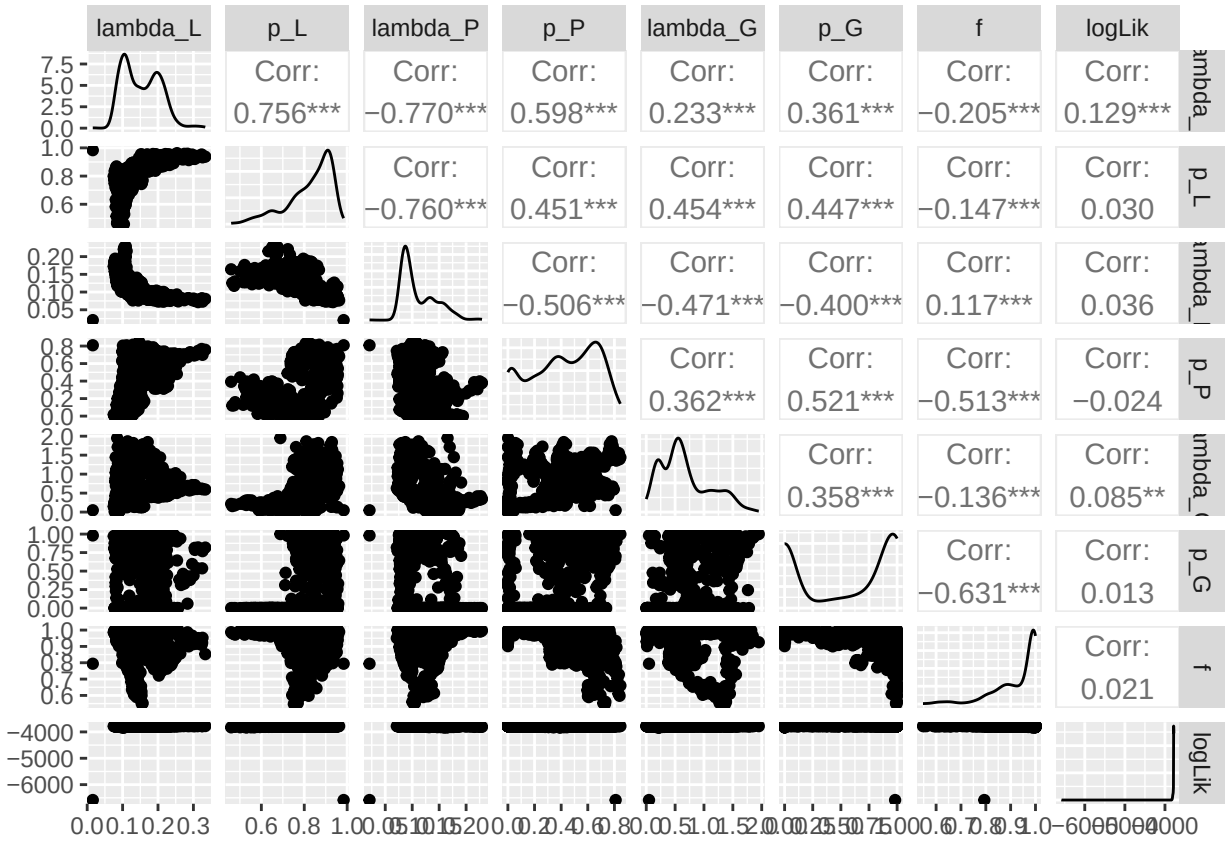



Correlations among the fitted parameters of the mechanistic model



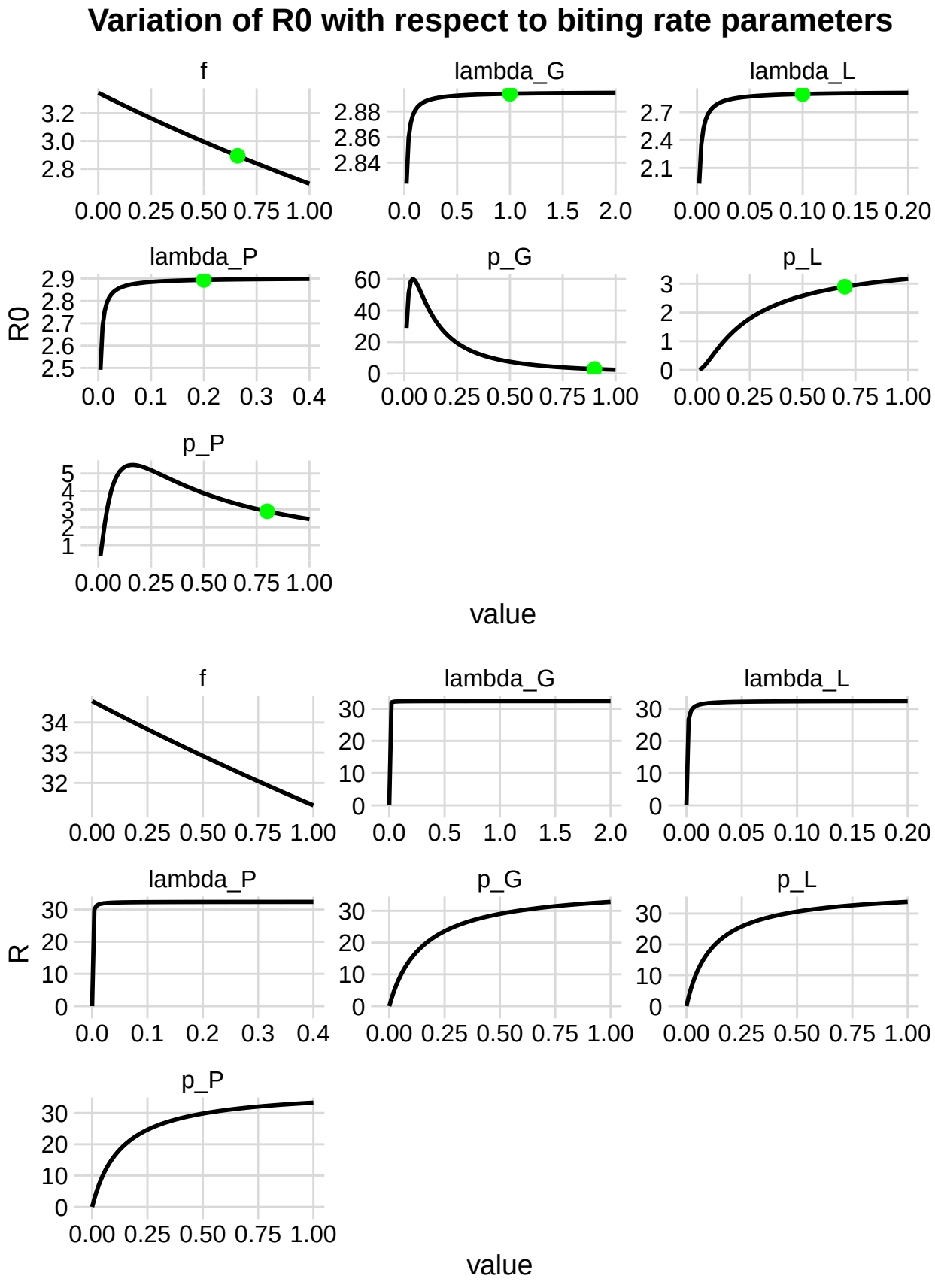
Scatter plots showing associations among mechanistic parameters

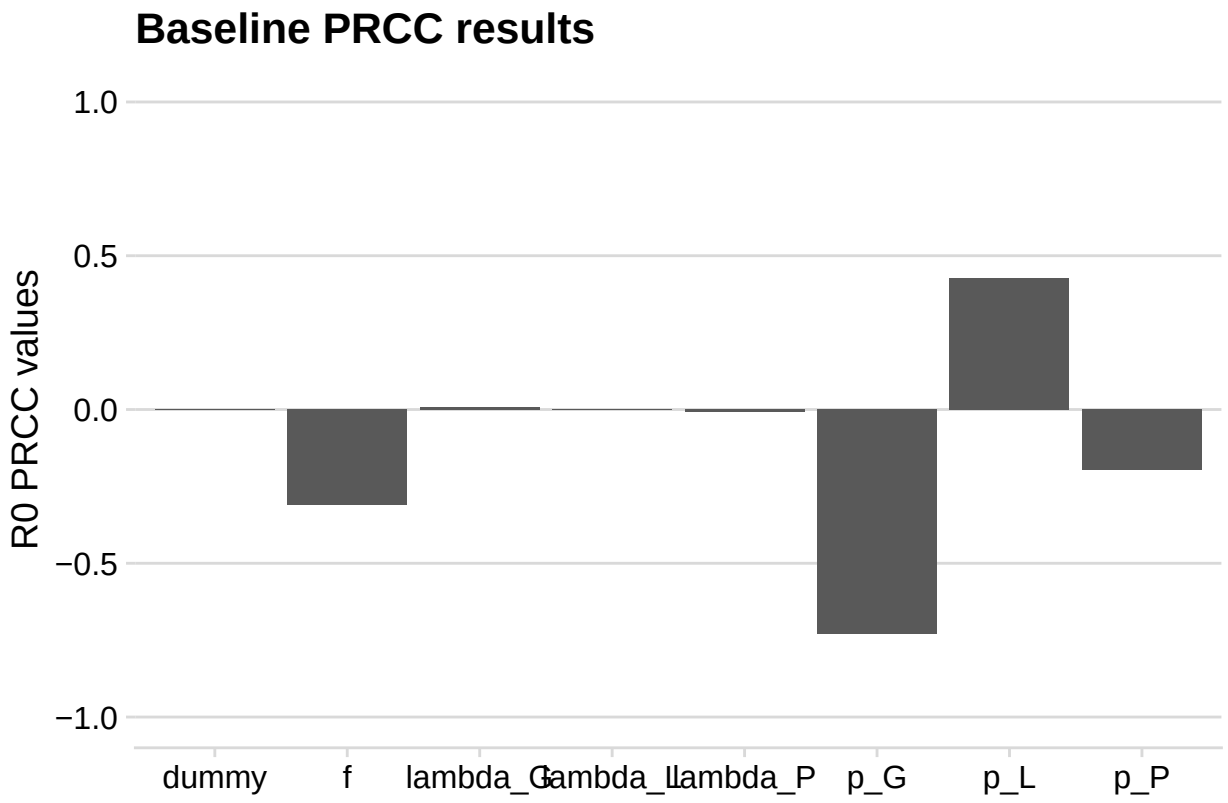


Blood-feeding and transmission

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

Sensitivity analysis with base and fitted parameters

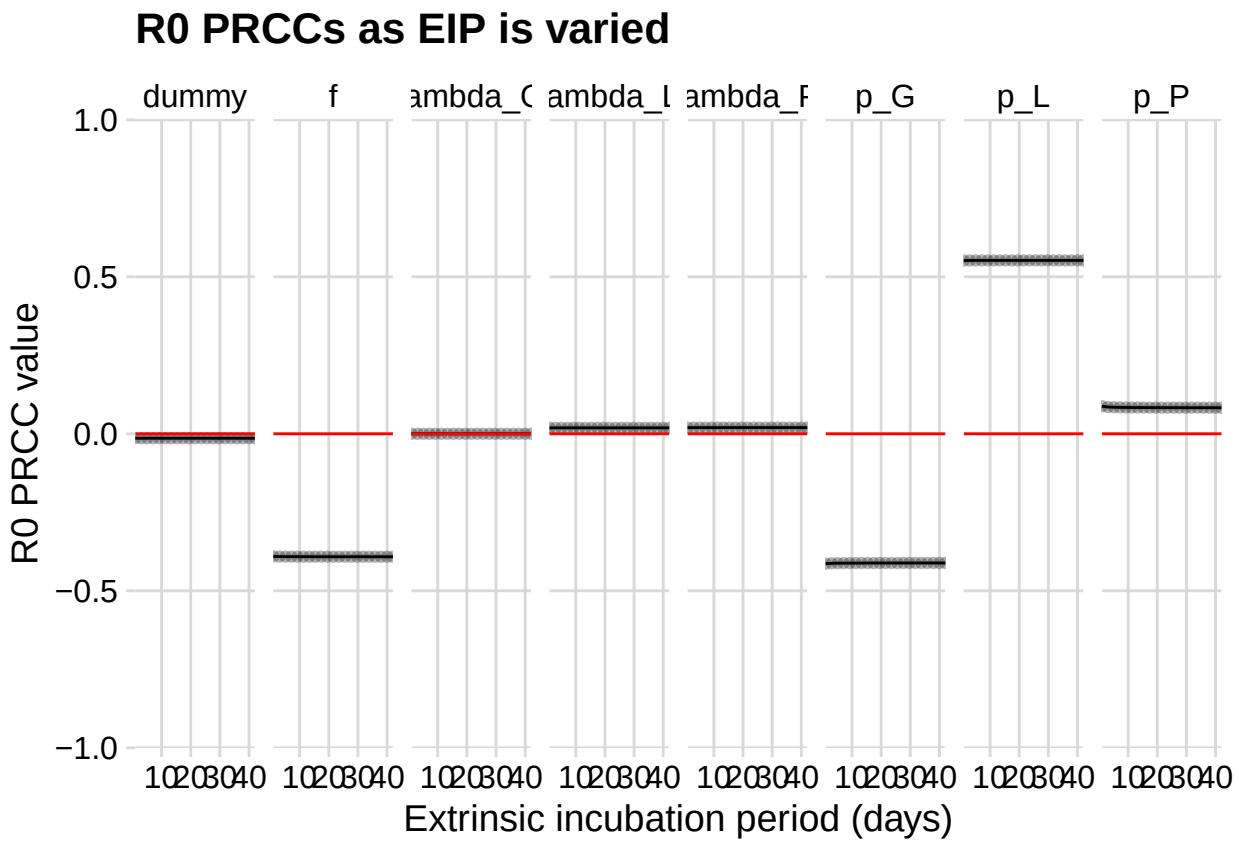




The global sensitivity of R_0 to the biting rate parameters does not change when the extrinsic incubation period is increased.

	used	(Mb)	gc trigger	(Mb)	max used	(Mb)
Ncells	2757194	147.3	5739105	306.6	5739105	306.6
Vcells	9234007	70.5	34666160	264.5	43332700	330.7

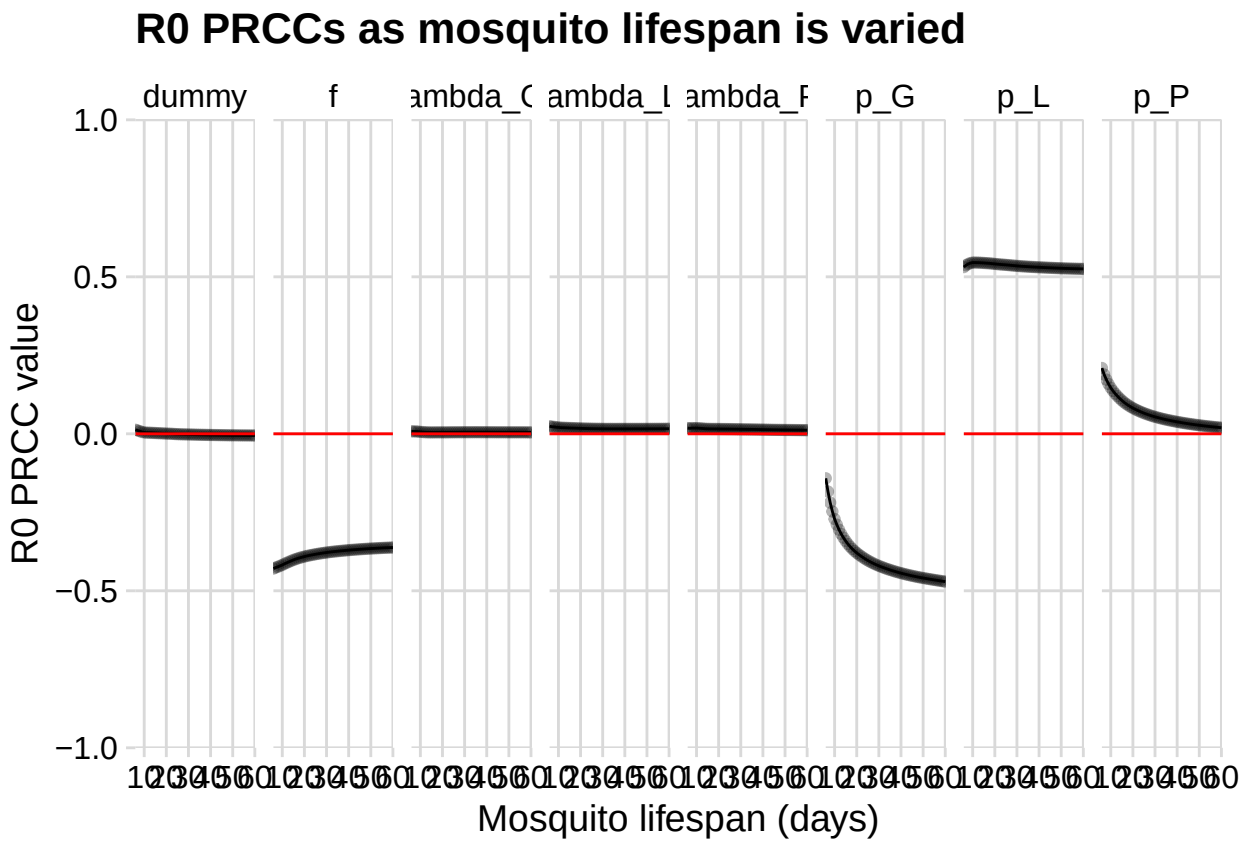
	used	(Mb)	gc trigger	(Mb)	max used	(Mb)
Ncells	2839809	151.7	5739105	306.6	5739105	306.6
Vcells	9416879	71.9	34666160	264.5	43332700	330.7



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

	used	(Mb)	gc trigger	(Mb)	max used	(Mb)
Ncells	2838256	151.6	5739105	306.6	5739105	306.6
Vcells	9413945	71.9	34666160	264.5	43332700	330.7

	used	(Mb)	gc trigger	(Mb)	max used	(Mb)
Ncells	2843885	151.9	5739105	306.6	5739105	306.6
Vcells	9434088	72.0	34666160	264.5	43332700	330.7


R0 PRCCs as mosquito lifespan is varied
dummy
f
ambda_C
ambda_L
ambda_P
p_G
p_L
p_P
1.0
0.5
0.0
−0.5
−1.0
R0 PRCC value
Mosquito lifespan (days)