

# 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  |
| $\lambda_L$ | Exit rate from landing stage (per minute)                          | 0.10  |
| $p_P$       | Probability of progressing from probing to ingesting               | 0.80  |
| $\lambda_P$ | Exit rate from probing stage (per minute)                          | 0.20  |
| $p_G$       | Probability of progressing from ingesting to ovipositing           | 0.90  |
| $\lambda_G$ | 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      |
|-------------|--------------------------------------|------------|
| $\eta$      | Extrinsic incubation rate            | 1.1570e-04 |
| $\mu$       | Mosquito mortality rate              | 3.3100e-05 |
| $\gamma$    | Return to blood-feeding rate         | 2.3150e-04 |
| $\gamma_H$  | Host recovery rate                   | 9.9200e-05 |
| $\mu_H$     | Host mortality rate                  | 0.0000e+00 |
| $K_H$       | Host carrying capacity               | 1.0000e+07 |
| $K_L$       | Larval mosquito carrying capacity    | 3.0000e+02 |
| $\rho_L$    | Larval mosquito maturation rate      | 5.7900e-05 |
| $\mu_L$     | Larval mosquito mortality rate       | 3.4700e-05 |
| $\varphi$   | Eggs per female per day              | 2.0833e-03 |
| $\beta_P$   | Probing transmission probability     | 1.0000e+00 |
| $\beta_G$   | Ingestion transmission probability   | 1.0000e+00 |
| $\beta_H$   | To-host transmission probability     | 1.0000e+00 |
| $\beta_V$   | To-mosquito transmission probability | 1.0000e+00 |
| $\lambda_Q$ | 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

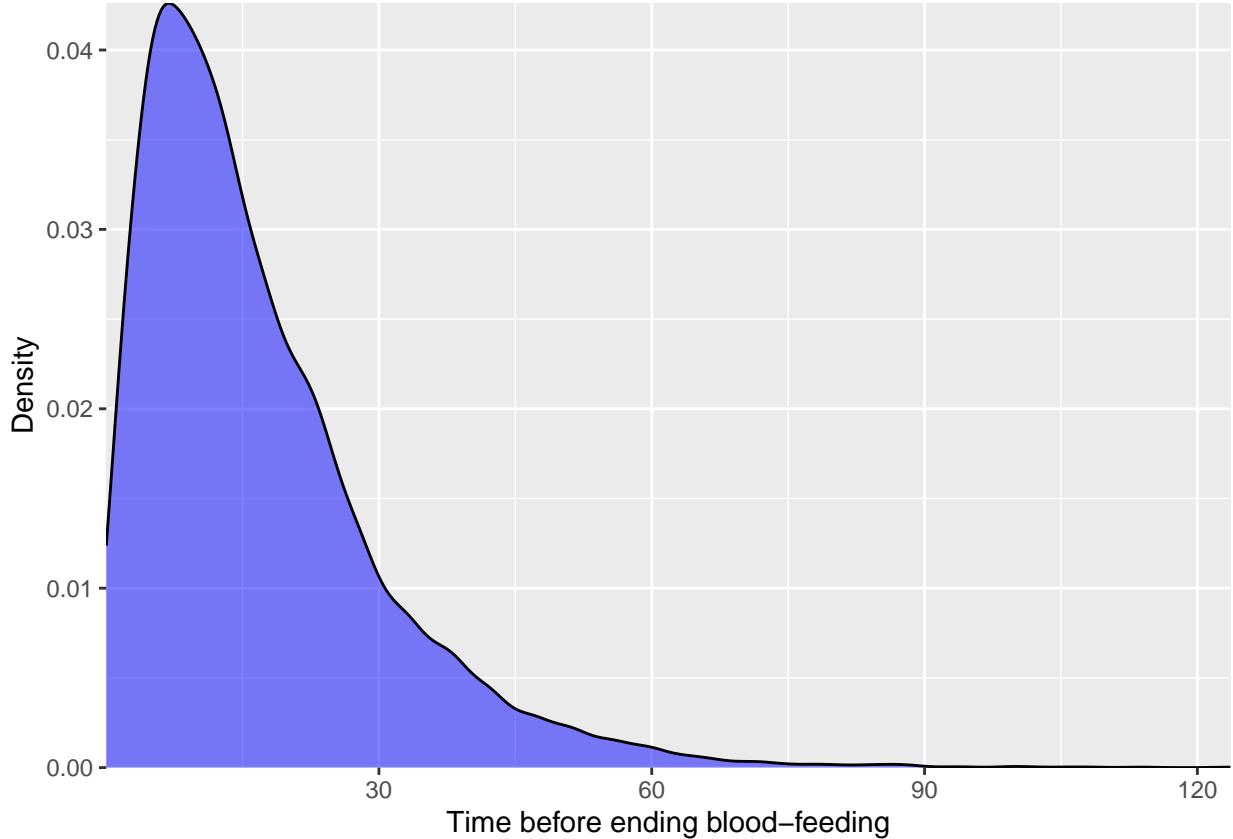
process. This simulation does not take into account the time that the mosquito spends questing, that is, we assume it has already located a suitable host to feed upon.

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 16.8149793 minutes and standard deviation of 13.2789815 minutes. The 5% and 95% quantiles are at 2.1959238 minutes and 42.73141 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  $A$ ).

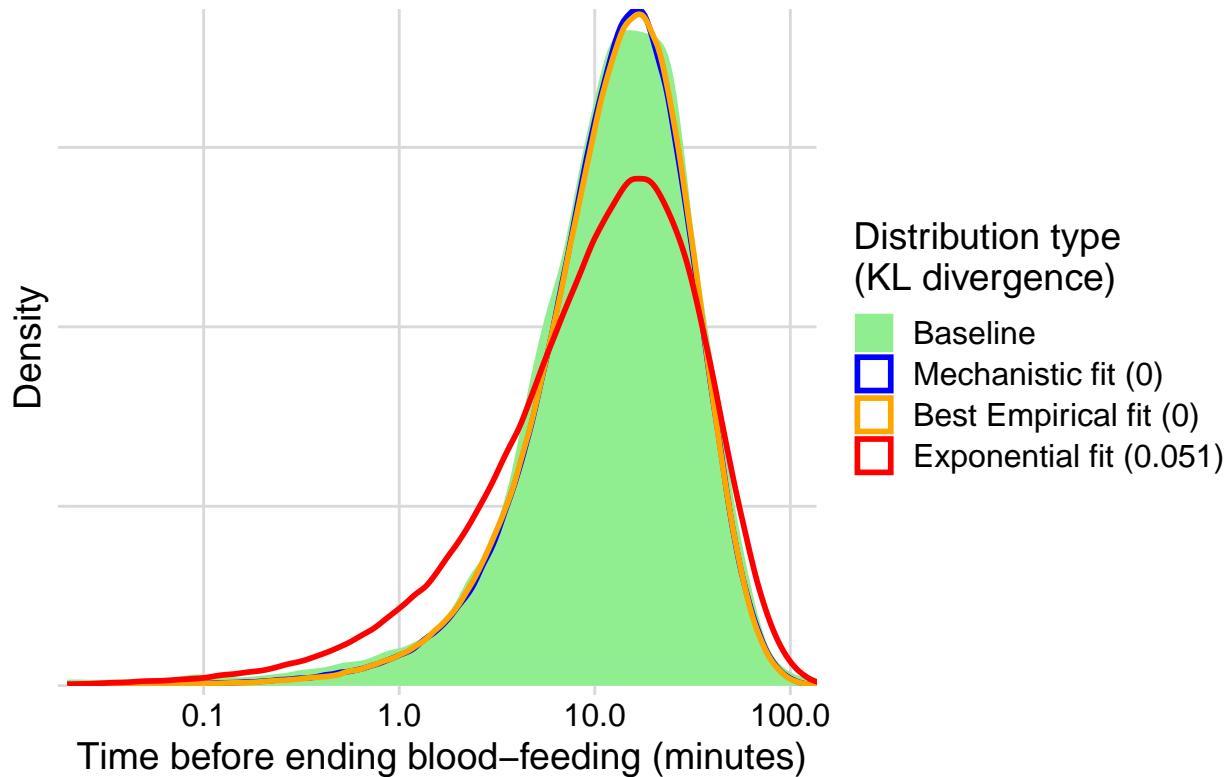
### Empirical model

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

### Mechanistic model

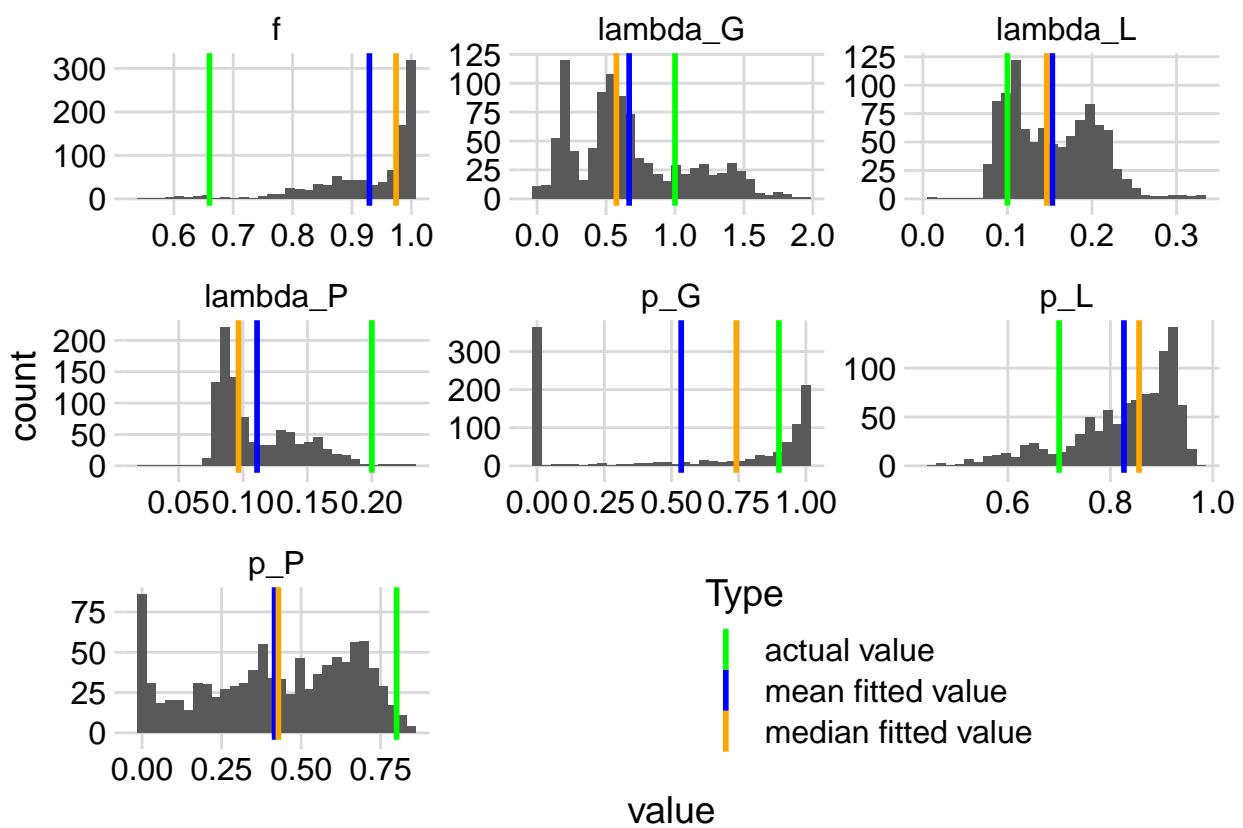
Now considering the mechanistic model. We will make direct comparisons between this model, the simulated data, and the empirical model. First, we look at how the waiting time statistics compare.

## Comparison of simulated and fitted blood-feeding waiting

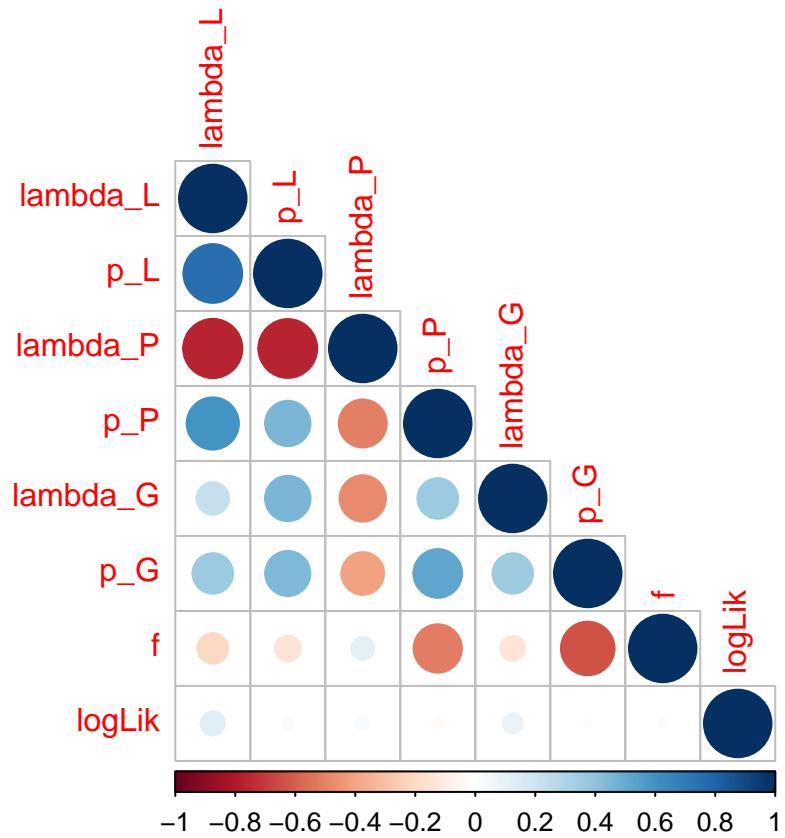


Distributions of the mechanistic parameters compared to the those used in the simulations.

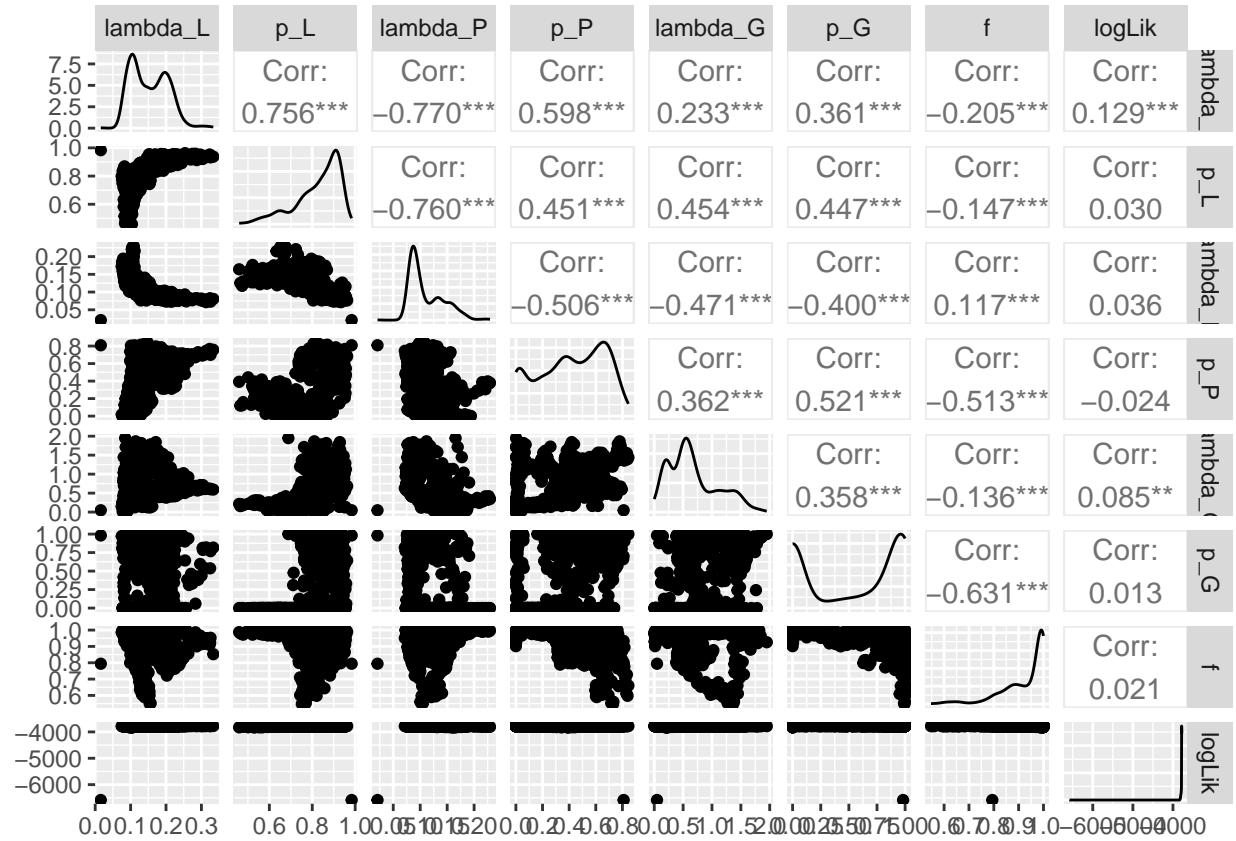
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## `stat_bin()` using `bins = 30`. Pick better value with `binwidth`.
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Correlations among the fitted parameters of the mechanistic model



Scatter plots showing associations among mechanistic parameters

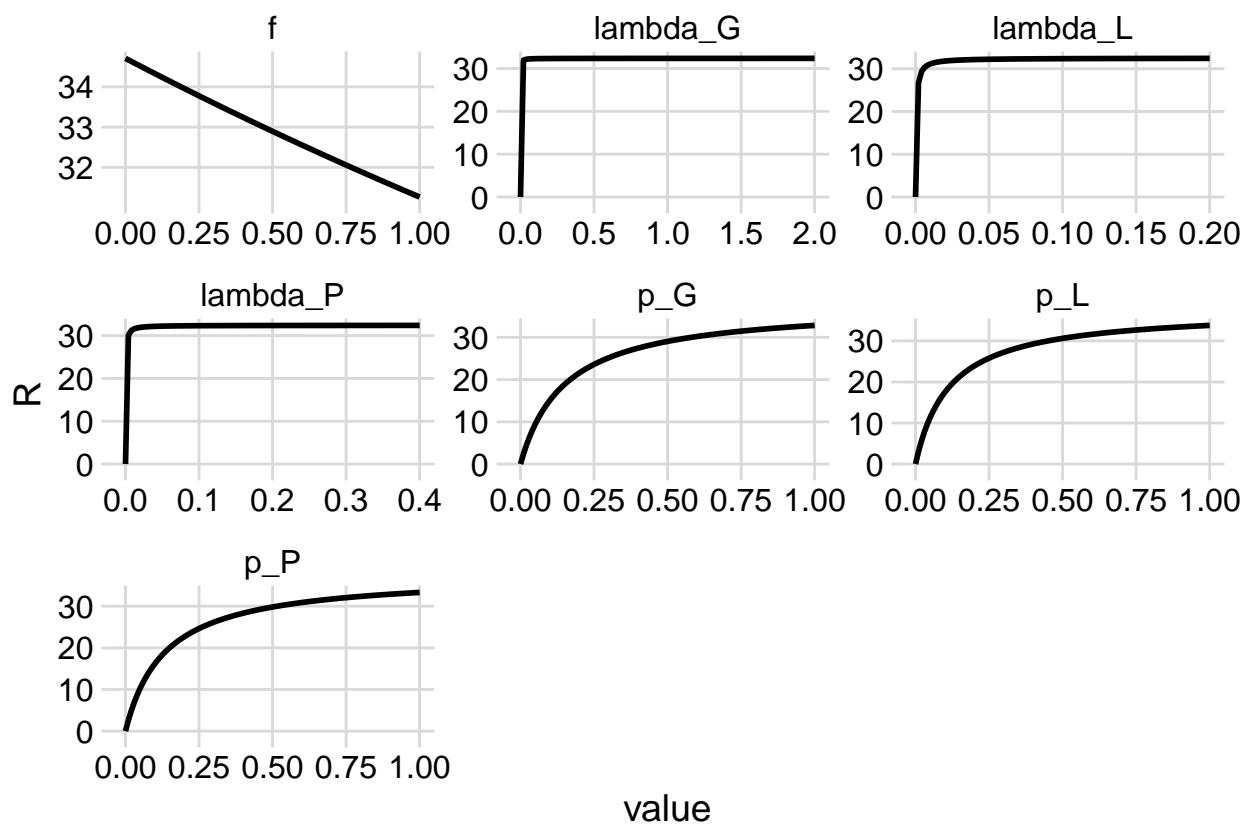
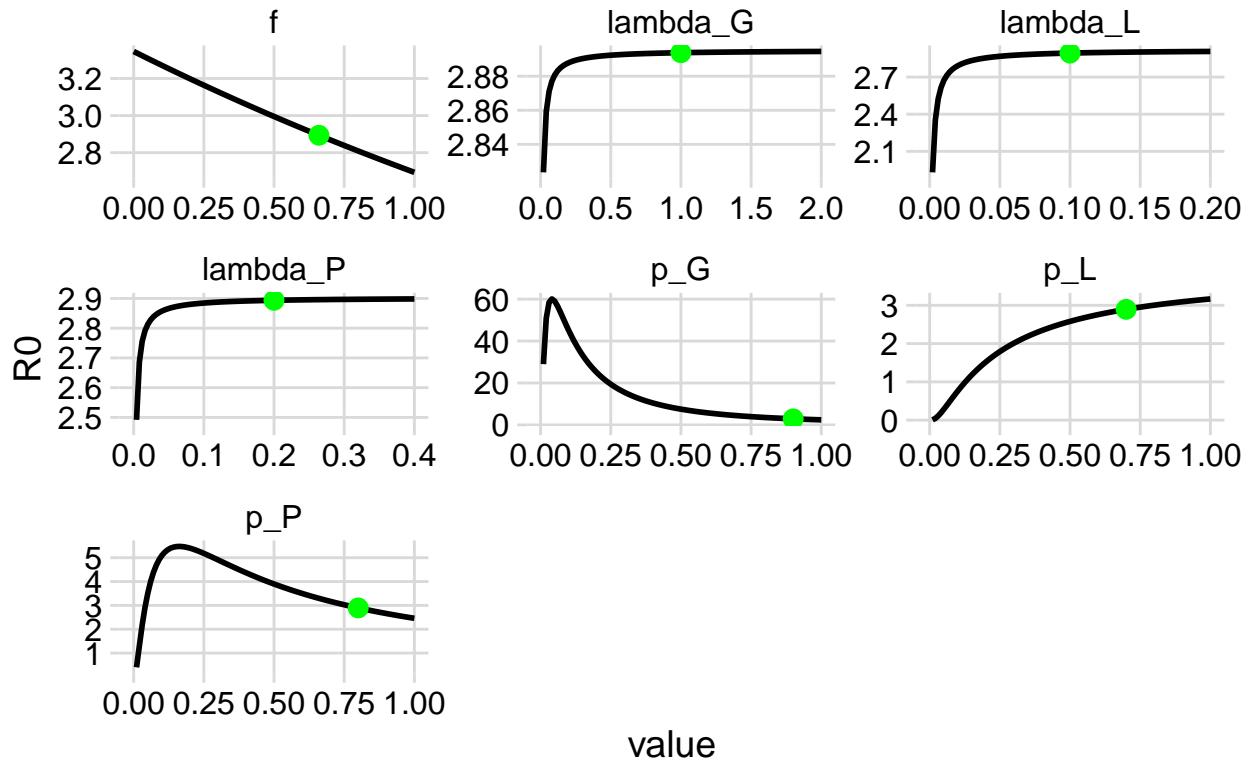


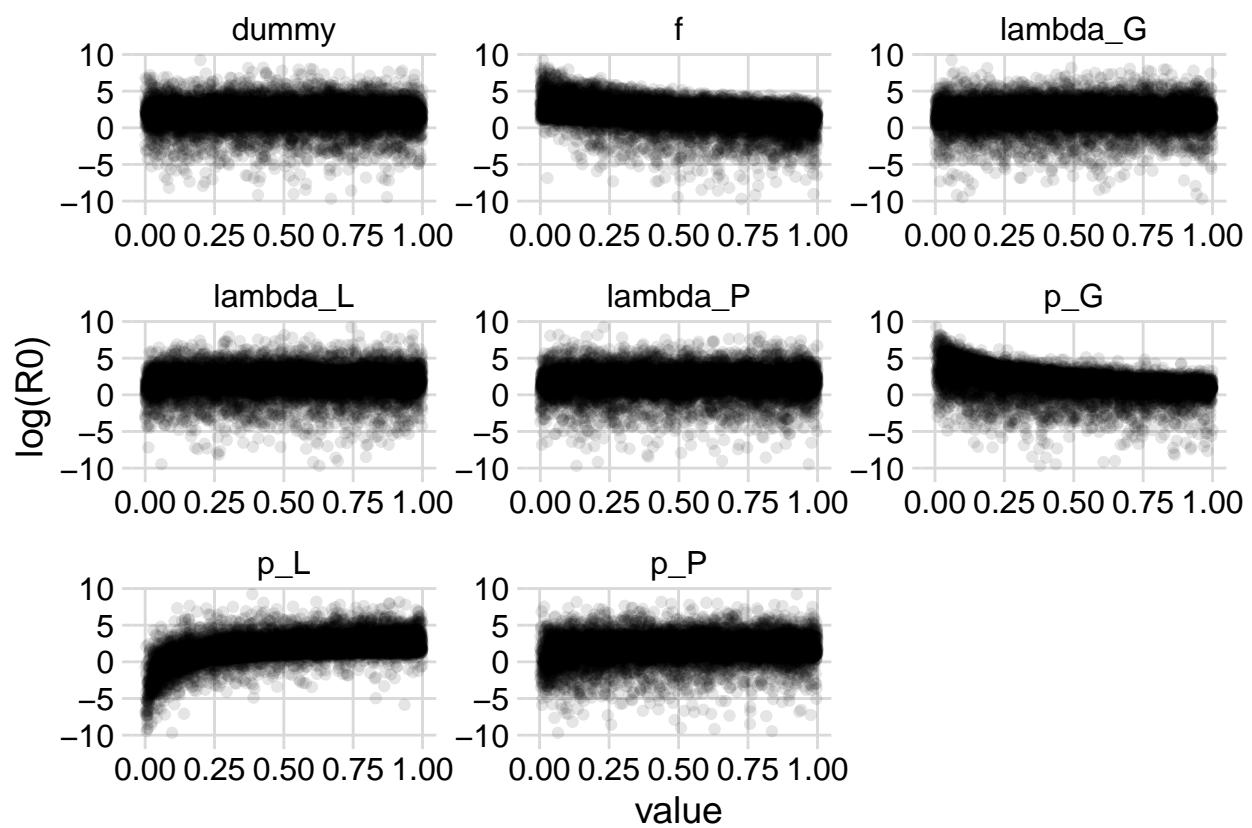
## Blood-feeding and transmission

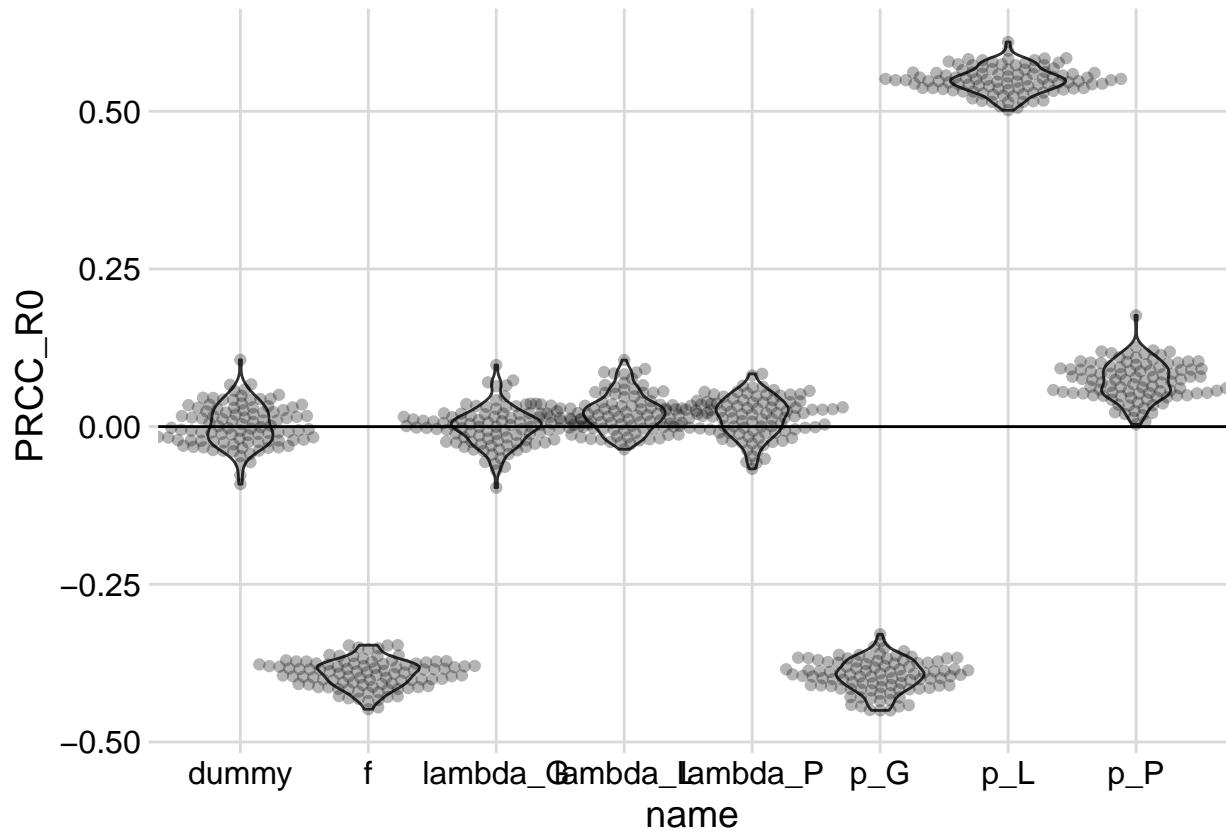
Here we study how the blood-feeding parameters affect transmission via the basic reproduction number.

## Sensitivity analysis with base and fitted parameters

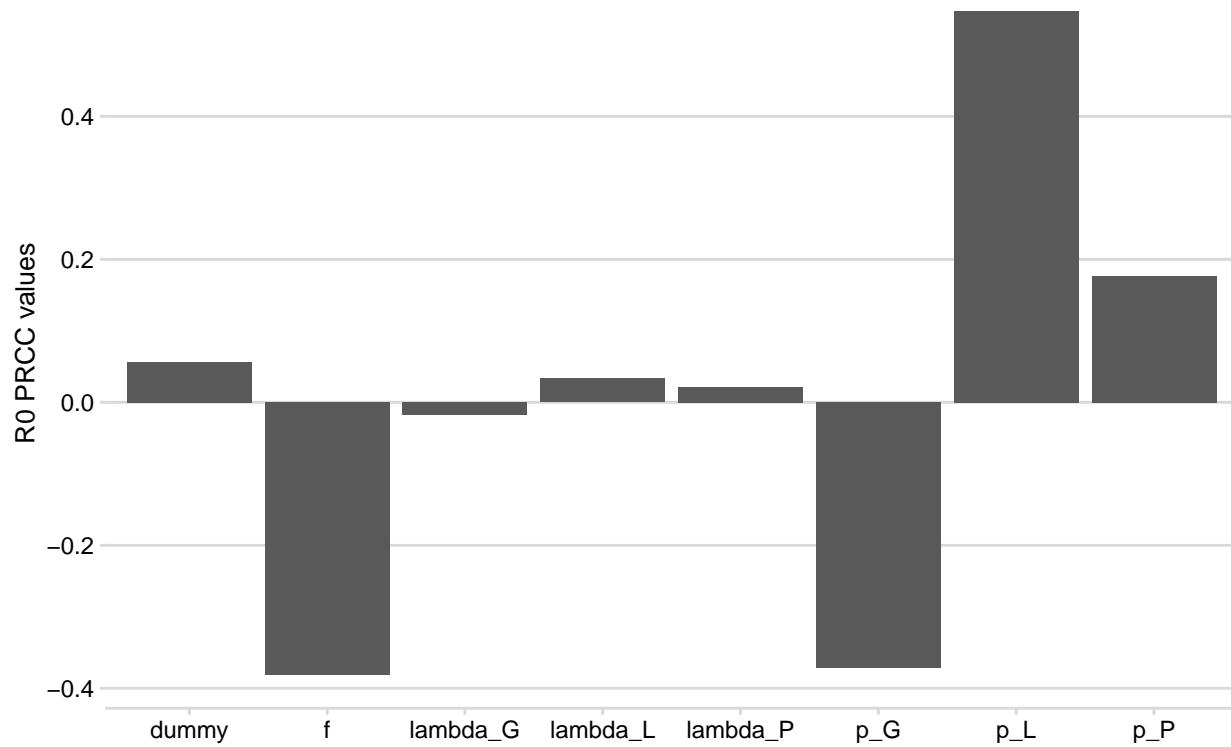
### Variation of R0 with respect to biting rate parameters



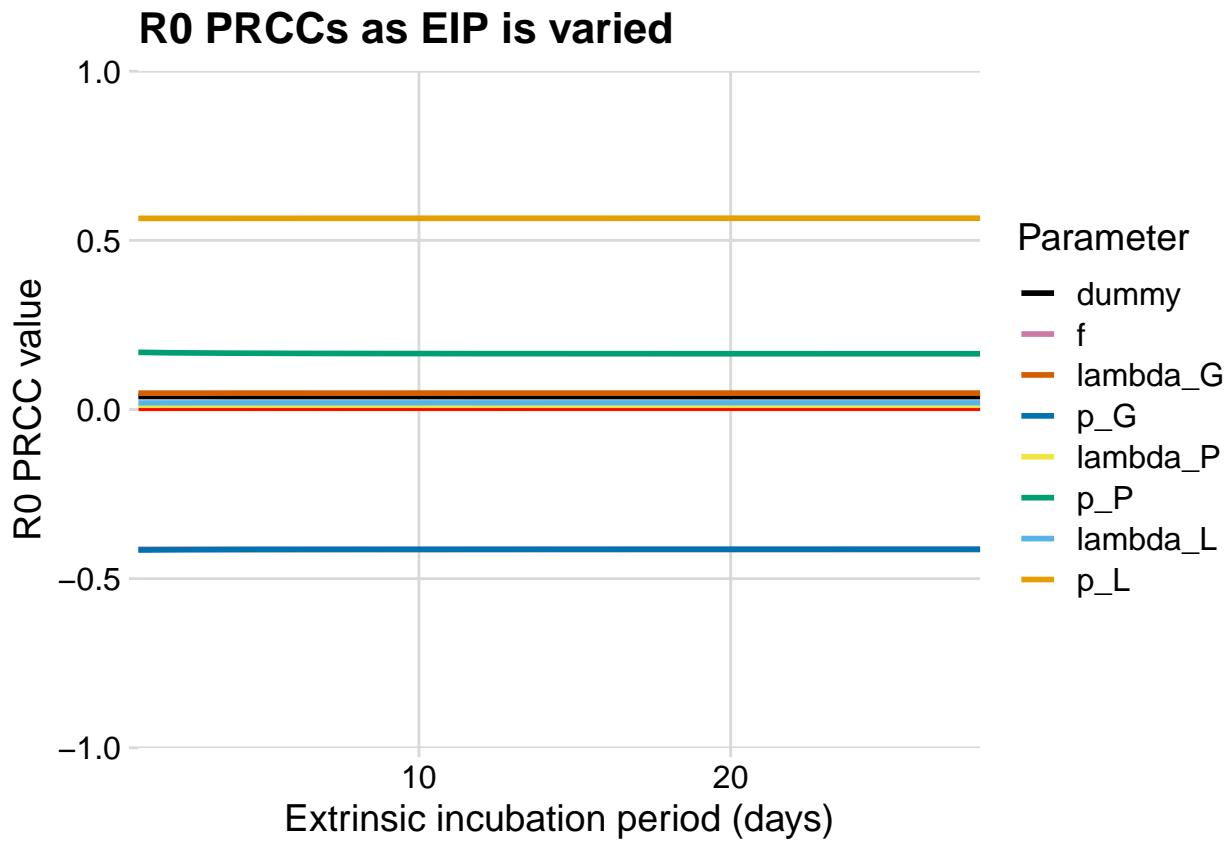




### Baseline PRCC results

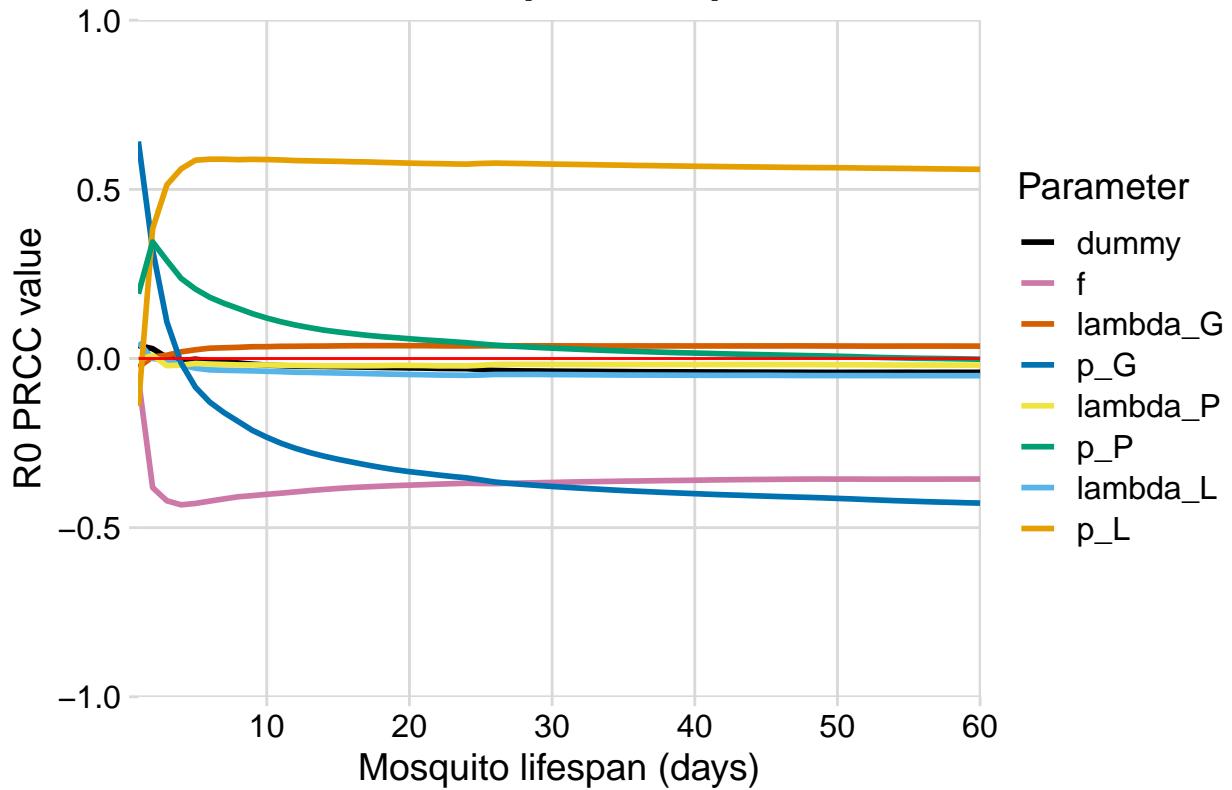


The global sensitivity of  $R_0$  to the biting rate parameters does not change when the extrinsic incubation period is increased.



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

## R<sub>0</sub> PRCCs as mosquito lifespan is varied



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

## R0 PRCCs as mosquito questing duration is varied

