deBInfer: Bayesian inference for dynamical models of biological systems in R

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Abstract

1. Understanding the mechanisms underlying biological systems, and ultimately, predicting their behaviours in a changing environment requires overcoming the gap between mathematical models and experimental or observational data. Differential equations (DEs) are commonly used to model the temporal evolution of biological systems, but statistical methods for comparing DE models to data and for parameter inference are relatively poorly developed. This is especially problematic in the context of biological systems where observations are often noisy and only a small number of time points may be available.

2. The Bayesian approach offers a coherent framework for parameter inference that can account for multiple sources of uncertainty, while making use of prior information. It offers a rigorous methodology for parameter inference, as well as modelling the link between unobservable model states and parameters, and observable quantities.

3. We present deBInfer, a package for the statistical computing environment R, implementing a Bayesian framework for parameter inference in DEs. deBInfer provides templates for the DE model, the observation model and data likelihood, and the model parameters and their prior distributions. A Markov chain Monte Carlo (MCMC) procedure processes these inputs to estimate the posterior distributions of the parameters and any derived quantities, including the model trajectories. Further functionality is provided to facilitate MCMC diagnostics and the visualisation of the posterior distributions of model parameters and trajectories.
4. The templating approach makes deBInfer applicable to a wide range of DE models. We demonstrate its application to ordinary and delay DE models for population ecology.

**Keywords:** parameter estimation; model calibration; ordinary differential equation; delay-differential equation; Markov chain Monte Carlo; chytridiomycosis;

1 **Introduction**

The use of differential equations (DEs) to model dynamical systems has a long and fruitful tradition in biological disciplines such as epidemiology, population ecology, and physiology ([Volterra 1926](#), [Kermack and McKendrick 1927](#)). As DE models are used in an attempt to understand biological systems, it is becoming clear that the simplest models cannot capture the rich variety of dynamics observed in them ([Evans et al. 2013](#)). However, more complex models come at the expense of additional states and/or parameters, and require more information for parameterization. Further, as most observational datasets contain uncertainty, model identification and fitting become increasingly difficult ([Lonergan et al. 2014](#)). Keeping complex models tractable and testable, and linking modeled quantities to data thus requires statistical methods of similar sophistication. This is particularly relevant in biology, where data series are often short or noisy, and where the scope for observational or experimental replication may be limited.

A vast array of analytical and numerical methods exists for solving DE models as well as exploring their properties and the effect of parameter values on their dynamics ([Jones 2003](#), [Smith 2011](#)). In some cases, parameters may be derived from first principles or measured directly, but often some or all parameters cannot be determined by either approach, and it is necessary to estimate them from an observational dataset.

A variety of parameter estimation approaches exists ([Brewer et al. 2008](#), [Aster et al. 2011](#)), although methods and computational tools for this purpose are much less well developed than the aforementioned system dynamics tools. Traditional parameter inference,
also known as “model calibration” or “solving inverse problems”, is often based on the maximum likelihood principle, which assumes the existence of a true model $M_{\text{true}}$ giving rise to a true dataset $Y_{\text{true}}$ such that

\[ M_{\text{true}}(\theta) = Y_{\text{true}}. \]  

(1)

The additional assumption that the observations $Y$ arise from a sum of $Y_{\text{true}}$ and measurement noise that is independently and normally distributed then leads to the least squares solution that is found by minimizing the Euclidean norm of the residual,

\[ ||M(\theta) - Y||_2. \]  

(2)

This approach allows for point estimates of the parameters, as well as the estimation of normal confidence intervals for the parameters and the correlations between them. However, these error bounds are local in nature and thus offer limited insight into the variability that is to be expected in the model outputs.

Bayesian approaches for parameter estimation in complex, nonlinear models have been established early on (e.g. [Tarantola and Valette 1982; Poole and Raftery 2000]) and they are being applied with increasing frequency to a broad range of biological models (e.g. [Coelho et al. 2011; Voyles et al. 2012; Johnson et al. 2013; Smith et al. 2015]). In the Bayesian approach the model, its parameters, and the data are viewed as random variables. This approach to parameter inference is attractive, as it provides a coherent framework that allows the incorporation of uncertainty in the observations and the process, and it relaxes the assumption of normal errors. It provides us not only with full probability distributions describing the parameters, but also with probability distributions for any quantity derived from them, including the model trajectories. Further, the Bayesian framework naturally lets us incorporate prior information about the parameter values. This is particularly useful when there are known biological or theoretical constraints on parameters. For example, many biological parameters, such as body size cannot take on
negative values. Using informative priors can help constrain the parameter space of the estimation procedure, aiding with parameter identifiability.

We explain the rationale behind the Bayesian approach below and describe our implementation of a fitting routine based on a Markov chain Monte Carlo (MCMC) sampler coupled to a numerical DE solver. We illustrate the application of deBInfer to a simple example, the logistic differential equation, as well as a more complex model of the reproductive life history of the fungal pathogen Batrachochytrium dendrobatidis.

2 Methods

The purpose of deBInfer is to estimate the probability distribution of the parameters of a user specified DE model $M$, given an empirical dataset $Y$, and accounting for the uncertainty in the data. The model takes the general form

$$M \equiv \frac{dx}{dt} = f(x_t, t, \theta)$$

(3)

where $x$ is a vector of variables evolving with time; $f$ is a functional operator that takes a time input and a vector of continuous functions $x_t(\theta)$ and generates the vector $\frac{dx}{dt}$ as output; and $\theta$ denotes a set of parameters. Further, we define $x_t(\tau) = x(t + \tau)$. When all $\tau \in \tau = 0$ the model is represented by a system of ordinary differential equations (ODEs), when any $\tau < 0$ the model is represented by a system of delay-differential equations (DDEs). For the purposes of inference $\tau$ is simply a subset of the parameters $\theta$ that are to be estimated. deBInfer implements inference for ODEs as well as DDEs with constant delays.

Using Bayes’s Theorem (Clark, 2007) we can calculate the posterior distribution of the model parameters, given the data and the prior information as

$$Pr(\theta|Y) = \frac{Pr(Y|\theta)Pr(\theta)}{\int Pr(Y|\theta)Pr(\theta)d\theta}$$

(4)
where $\Pr()$ denotes a probability, $\mathcal{Y}$ denotes the data, and $\theta$ denotes the set of model parameters. The product in the numerator is the *joint distribution*, which is made up of the *likelihood* $\Pr(\mathcal{Y}|\theta)$ or $L(\mathcal{Y}|\theta)$, which gives the probability of observing $\mathcal{Y}$ given the deterministic model $\mathcal{M}(\theta)$, and the *prior distribution* $\Pr(\theta)$, which represents the knowledge about $\theta$ before the data were collected. The denominator represents the marginal distribution of the data $\Pr(\mathcal{Y}) = \int \Pr(\mathcal{Y}|\theta) \Pr(\theta) d\theta$. Before the data are collected $\mathcal{Y}$ is a random variable, but after they are collected the marginal distribution becomes a fixed quantity. This means, the inferential problem reduces to

$$\Pr(\theta|\mathcal{Y}) \propto \Pr(\mathcal{Y}|\theta) \Pr(\theta). \tag{5}$$

That is, finding a specific proportionality that allows the *posterior* $\Pr(\theta|\mathcal{Y})$ to be a proper probability density (or mass) function that integrates to 1.

Closed form solutions for the posterior are practically impossible to obtain for complex non-linear models with more than a few parameters, but they can be approximated, e.g. by combining the MCMC algorithm with a Metropolis-Hastings sampler [Clark 2007]. This yields a sequence of likelihoods that follow a frequency distribution which approximates the posterior distribution.

The likelihood $L(\mathcal{Y}|\theta)$ describes the probability of the data for a given realization of the model $\mathcal{M}(\theta)$, and we can use the fact that the data are uncertain to derive an expression like

$$L(\mathcal{Y}|\theta) = \prod_t \mathcal{P}(\mathcal{Y}_t, \mu = \mathcal{Y}_t(\theta), \sigma^2 = \mathcal{V}_t) \tag{6}$$

where $\mathcal{P}$ is a parametric probability distribution, typically with first and second moments $\mu$ and $\sigma^2$, $\mathcal{Y}_t$ is data item $t$, and $\mathcal{V}_t$ is the variance associated with $\mathcal{Y}_t$.

Often the data $\mathcal{Y}$ contain multiple data series, e.g. time-course observations of different state variables, following different probability distributions. In this case the likelihood becomes the product over all series and each data item in each series.
\[ L(Y|\theta) = \prod_s \prod_t \mathcal{P}_s(Y_{s,t}, \mu_s = Y_{s,t}(\theta), \sigma^2_s = V_{s,t}). \] 

(7)

3 Implementation

debInfer provides a framework for dynamical models consisting of a deterministic DE model and a stochastic observation model. In order to perform inference using debInfer, the user must specify: the DE model; an observation model, and thus the data likelihood; and declare all model and observation parameters, including prior distributions for those parameters that are to be estimated. debInfer takes these inputs and performs MCMC to sample from the posterior distributions of parameters, solving the DE model numerically within the MCMC procedure. The MCMC procedure for debInfer offers independent, as well as random-walk Metropolis-Hastings updates and is implemented fully in R [R Core Team 2015]. Background on Metropolis-Hastings MCMC are widely available in the literature (e.g. Clark 2007; Brooks et al. 2011).

Table 1: Implementation of the random-walk Metropolis-Hastings algorithm. The transition from a parameter value \( \theta^{(k)} \) in the Markov chain at step \( k \) to its value at step \( k + 1 \) proceeds via the outlined steps. \( q \) is a conditional density, the so called proposal distribution.

1. Generate a proposal \( \theta^{(*)} \sim q(\theta^{(*)} | \theta^{(k)}) \)
2. Evaluate the prior probability \( \Pr(\theta^{(*)}) \)
3. if \( \Pr(\theta^{(*)}) = 0 \)
   Let \( \theta^{(k+1)} \leftarrow \theta^{(k)} \)
4. if \( \Pr(\theta^{(*)}) \neq 0 \)
   if \( \theta \in \Theta_{DE} \); solve the DE model
   Let \( \theta^{(k+1)} \leftarrow \begin{cases} \theta^{(*)} & \text{with probability } \rho(\theta^{(k)}, \theta^{(*)}) , \\ \theta^{(k)} & \text{with probability } 1 - \rho(\theta^{(k)}, \theta^{(*)}), \end{cases} \)
   where \( \rho(\theta^{(k)}, \theta^{(*)}) = \min \left\{ \frac{\Pr(\theta^{(*)} | Y)}{\Pr(\theta^{(k)} | Y)} \cdot \frac{q(\theta^{(k)} | \theta^{(*)})}{q(\theta^{(*)} | \theta^{(k)})}, 1 \right\} \)
As numerically solving the DE model is the most computationally costly step, we made two slight modifications to the basic Metropolis-Hastings algorithms. (i) deBInfer makes a distinction between the parameters of the DE model $\theta_{DE}$, and the observation parameters $\theta_{obs}$, invoking the solver only for updates of the former, and (ii) the prior probability of each parameter proposal from the random walk sampler is evaluated before the posterior density and the acceptance ratio are calculated. This allows the rejection of proposals outside the prior support without invoking the numerical solver. The algorithm is outlined in Table 1.

deBInfer provides a choice of three proposal distributions $q$ for the first step in the algorithm, a normal $N(\theta^{(k)}, \sigma_{prop}^2)$, an asymmetric uniform $U(\frac{a}{b}\theta^{(k)}, \frac{b}{a}\theta^{(k)})$ and a multivariate normal $N(\theta^{(k)}, \Sigma)$. deBInfer requires manual tuning, i.e. the variance components $\sigma_{prop}^2$, $a$, $b$, and $\Sigma$, respectively, are user specified inputs. The asymmetric uniform distribution is useful for proposals of parameters that are strictly positive, such as variances, and the multivariate normal is useful for efficiently sampling parameters that are strongly correlated, as is often the case for DE model parameters.

4 A simple example - logistic population growth

We illustrate the steps needed to perform inference for a DE model, by conducting inference on the logistic model (acknowledging that the existence of a closed form solution to this DE makes this an artificial example):

$$\frac{dN}{dt} = rN \left(1 - \frac{N}{K}\right).$$

Annotated code to implement this model, simulate observations from it, and conduct the inference is provided as a package vignette (Appendix A). An overview of the core functions available in deBInfer is provided in Table 2.
Table 2: An overview of the main functions available in deBInfer.

| Function             | Description                                                                 |
|----------------------|-----------------------------------------------------------------------------|
| `debinfer_par`       | creates a data structure representing an individual parameter or initial    |
|                      | value of the DE model, or an observation parameter, and the corresponding  |
|                      | values, priors, etc.                                                        |
| `setup_debinfer`     | combines multiple parameter declarations into an input object for inference |
| `de_mcmc`            | conducts MCMC inference on a DE model and returns an object of the class    |
|                      | `debinfer_result`.                                                          |
| `plot.debinfer_result` | Plots traces and posterior densities (wrapper for `coda::plot.mcmc`).    |
| `summary.debinfer_result` | Summary statistics for MCMC samples (wrapper for `coda::summary.mcmc`). |
| `pairs.debinfer_result` | Pairwise plots and correlations of marginal posterior distributions.       |
| `post_prior_densplot` | Overlay of posterior and prior densities for free parameters.             |
| `post_sim`           | Simulate posterior trajectories of the DE model and summary statistics     |
|                      | thereof.                                                                    |
| `plot.post_sim_list` | Plot posterior DE model trajectories.                                       |

4.1 Installation

The deBInfer package can be installed directly from github using devtools ([Wickham and Chang, 2016](#)), which can be installed from CRAN.

```r
#Install the devtools package.
install.packages("devtools")
#Install and load deBInfer.
devtools::install_github("pboesu/debinfer")
library(deBInfer)
```

4.2 Specification of the differential equation model

deBInfer makes use of the deSolve and PBSddesolve packages ([Soetaert et al., 2010](#), [Couture-Beil et al., 2014](#)) to numerically solve ODE and DDE models. The DE model has to be specified as a function containing the model equations, following the guidelines given in the respective package documentations. For our simple example the function takes three inputs: time, a vector of time points at which to evaluate the DE, y, a vector
containing the initial value for the state variable \( N \), and \( \text{parms} \), a vector containing the parameters \( r \) and \( K \).

\[
\text{logistic\_model} \leftarrow \text{function}(\text{time}, y, \text{parms}) \{ \\
\quad \text{with(as.list(c(y, parms))}, \{ \\
\quad\quad dN \leftarrow r \times N \times (1 - N / K) \\
\quad\quad \text{list}(dN) \\
\quad\}\} \\
\}
\]

4.3 Observation model and likelihood specification

For the purpose of demonstration we will conduct inference on simulated observations from this model assuming log-normal noise with a standard deviation \( \sigma_{\text{obs}}^2 \). A set of simulated observations is provided with the package and can be loaded with the command `data(logistic)`. The appropriate log-likelihood takes the form

\[
\ell(Y|\theta) = \sum_t \ln \left( \frac{1}{\tilde{N}_t \sigma_{\text{obs}} \sqrt{2\pi}} \exp \left( - \frac{(\ln \tilde{N}_t - \ln(N_t + \epsilon))^2}{2\sigma_{\text{obs}}^2} \right) \right) \tag{9}
\]

where \( \tilde{N}_t \) are the observations, and \( N_t \) are the predictions of the DE model given the current MCMC sample of the parameters \( \theta \). Further, \( \epsilon \) is a small correction needed, because the DE solution can equal zero (or less, depending on numerical precision). We chose \( \epsilon = 10^{-6} \), which is on the same order as the numerical precision of the default solver (`deSolve::ode with method = "lsoda"`).

The `deBInfer` observation model template requires three inputs: a `data.frame` of observations, `data`; the simulated trajectory returned by the numerical solver in MCMC procedure, `sim.data`; and the current sample of the parameters, `samp`. The user specifies the observation model such that it returns the summed log-likelihoods of the data. In this example the observations are in the data.frame column `N_noisy`, and the corresponding predicted states are in the column `N` of the matrix-like object `sim.data` (see Appendix A).
```r
# load example data
data(logistic)

# user defined data likelihood
logistic_obs_model <- function(data, sim.data, samp){
  epsilon = 1e-6
  llik <- sum(dlnorm(data$N_noisy, meanlog=log(sim.data[, "N"]+epsilon),
                   sdlog=samp[["sdlog.N"]], log=TRUE))
  return(llik)
}
```

### 4.4 Parameter, prior, and sampler specification

All parameters that are used in the DE model and the observation model need to be declared for the inference procedure using the `debinfer_par()` function. The declaration describes the variable name, whether it is a DE or observation parameter and whether or not it is to be estimated. If the parameter is to be estimated, the user also needs to specify a prior distribution and a number of additional parameters for the MCMC procedure. `debinfer` currently supports priors from all probability distributions implemented in base R, as well as their truncated variants, as implemented in the `truncdist` package [Novomestky and Nadarajah, 2012].

We declare the DE model parameter $r$, assign a prior $r \sim \mathcal{N}(0, 1)$ and a random walk sampler with a Normal kernel (`samp.type="rw"`) and proposal variance of 0.005 with the command

```r
r <- debinfer_par(name = "r", var.type = "de", fixed = FALSE,
                  value = 0.5, prior="norm", hypers=list(mean = 0, sd = 1),
                  prop.var=0.005, samp.type="rw")
```

Similarly, we declare $K \sim \mathcal{N}(1, 1)$ and $\ln(\sigma_{obs}^2) \sim \mathcal{N}(0, 1)$.

```r
K <- debinfer_par(name = "K", var.type = "de", fixed = FALSE,
                  value = 0.5, prior="norm", hypers=list(mean = 0, sd = 1),
                  prop.var=0.005, samp.type="rw")
```
value = 5, prior="lnorm", hypers=list(meanlog = 1, sdlog = 1),
prop.var=0.1, samp.type="rw")

sdlog.N <- debinfer_par(name = "sdlog.N", var.type = "obs", fixed = FALSE,
value = 0.1, prior="lnorm", hypers=list(meanlog = 0, sdlog = 1),
prop.var=c(3,4), samp.type="rw-unif")

Note that we are using the asymmetric uniform proposal distribution for the variance
parameter (samp.type="rw-unif"), as this ensures strictly positive proposals. Lastly, we
provide an initial value $N_0 = 0.1$ for the DE:

N <- debinfer_par(name = "N", var.type = "init", fixed = TRUE, value = 0.1)

4.5 MCMC inference

The MCMC procedure is called using the function de_mcmc() which takes the declared
parameters, the DE and observational models, the data, and further optional arguments
to the MCMC procedure and/or the solver as inputs and returns an array containing the
resulting MCMC samples.

All declared parameters are collated using setup_debinfer()

mcmc.pars <- setup_debinfer(r, K, sdlog.N, N)

and passed to de_mcmc() which is set to use deSolve::ode() as a backend in this case,
as specified by the argument solver = "ode"

# do inference with deBInfer
# MCMC iterations
iter = 5000

# inference call
mcmc_samples <- de_mcmc(N = iter, data=logistic, de.model=logistic_model,
obs.model=logistic_obs_model, all.params=mcmc.pars,
\[ T_{\text{max}} = \max(\text{logistic$\times$time}), \text{data.times=logical$\times$time}, \]
\[ \text{cnt=500, plot=FALSE, solver="ode"} \]

4.6 Inference Outputs

The inference function returns an object of class `debinfer_result`, which contains the posterior samples in a format compatible with the `coda` package (Plummer et al., 2006), as well as the DE and observation models and all parameters used for inference. This allows the use of the diagnostic functions and plotting routines provided in `coda` (see Fig. 1). We also provide additional functions and methods such as `pairs.debinfer_result()` to create pairwise plots of the marginal posterior distributions, which show correlations between individual parameters (see Fig. 2), `post_prior_densplot()`, which allows a visual comparison between prior and marginal posterior densities for each parameter, `post_sim()` which simulates posterior model trajectories and associated credible intervals, as well as plotting methods for the latter (see Fig. 3).

5 Example application - DDE model of fungal population growth

To illustrate applications of `deBInfer` beyond the simplistic example above, we outline inference procedures for a more complex model and corresponding observational data. Full model details and annotated code can be found in Appendix B.

Our example demonstrates parameter inference for a DDE model of population growth in the environmentally sensitive fungal pathogen *Batrachochytrium dendrobatidis* (Bd), which causes the amphibian disease chytridiomycosis (Rosenblum et al., 2010; Voyles et al., 2012). This model has been used to further our understanding of pathogen responses to changing environmental conditions. Further details about the model development, and the experimental procedures yielding the data used for parameter inference can be found in Voyles et al. (2012).
Figure 1: MCMC traces and posterior density plots for the logistic model. Figures like this one can be created using `plot.debinfer_result`.

Figure 2: Pairwise plot of the marginal posterior distributions. This figure was created using `pairs.debinfer_result`. 

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Figure 3: Posterior model trajectory (median with 95% highest posterior density interval), created with plot.post_sim.list, and the data points used for fitting.

The model follows the dynamics of the concentration of an initial cohort of zoospores, $C$, the concentration of zoospore-producing sporangia, $S$, and the concentration of zoospores in the next generation $Z$. The initial cohort of zoospores, $C$, starts at a known concentration, and zoospores in this initial cohort settle and become sporangia at rate $s_r$, or die at rate $\mu_Z$. $f_s$ is the fraction of sporangia that survive to the zoospore-producing stage. We assume that it takes a minimum of $T_{\text{min}}$ days before the sporangia produce zoospores, after which they produce zoospores at rate $\eta$. Zoospore-producing sporangia die at rate $d_s$. The concentration of zoospores, $Z$, is the only state variable measured in the experiments, and it is assumed that these zoospores settle ($s_r$) or die ($\mu_Z$) at the same rates as the initial cohort of zoospores. The equations that describe the population dynamics are as follows:

\[
\frac{dC}{dt} = -(s_r + \mu_Z)C(t) \tag{10}
\]
\[
\frac{dS}{dt} = s_r f_s C(t - T_{\text{min}}) - d_s S(t) \tag{11}
\]
\[
\frac{dZ}{dt} = \eta S(t) - (s_r + \mu_Z)Z(t) \tag{12}
\]
Figure 4: Comparison of marginal posterior densities (black) and the corresponding priors (red) of the estimated parameters of the chytrid model. This plot was created using post_prior_densplot.

Because the observations are counts of zoospores (i.e. discrete numbers), we assume that observations of the system at a set of discrete times $t'$ are independent Poisson random variables with a mean given by the solution of the DDE, at times $t'$. The log-likelihood of the data given the parameters, underlying model, and initial conditions is then a sum over the $n$ observations at each time point in $t'$

$$
\ell(Z|\theta) = \sum_{t}^{n} Z_t \log \lambda - n\lambda
$$

(13)

In this case we conduct inference using deSolve::dede() as the backend to de_mcmc. The marginal posteriors of the estimated parameters are presented in Fig. 4 and posterior trajectories for the model are presented in Fig. 5.
Figure 5: Posterior trajectories for each state variable of the chytrid model based on 1000 model simulations from the posterior of the parameters and the data points $Z_{\text{obs}}$ used for fitting.

6 Known limitations

The MCMC sampler is implemented in R, which makes it considerably slower than samplers written in compiled languages e.g., those underlying packages such as Stan \cite{carpenter2016stan} or Filzbach\footnote{http://research.microsoft.com/en-us/um/cambridge/groups/science/tools/filzbach/filzbach.htm}. Furthermore, the \texttt{debinfer} MCMC algorithm is not adaptive and requires manual tuning. Nonetheless, the package is able to fit real world problems in a matter of minutes to hours on current desktop hardware, which is acceptable for many applications. It also provides more flexibility than other packages. For example, Stan currently only provides inference for ODE models, but not DDE models.
7 Conclusion

Understanding the mechanisms underlying biological systems, and ultimately, predicting their behaviours in a changing environment requires overcoming the gap between mathematical models and experimental or observational data. We believe that Bayesian inference provides a powerful tool for fitting dynamical models and selecting between competing models. The deBInfer R package provides a suite of tools to this end in a programming language that is widespread in many biological disciplines. We hope that our package, will lower the hurdle to the uptake of this inference approach for empirical biologists. We encourage users to report bugs and provide other feedback on the project issue page: https://github.com/pboesu/debinfer/issues

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9 Data Accessibility

All data used in this article are included in the deBInfer package and its vignettes, which are freely available from https://github.com/pboesu/debinfer.

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A  **Annotated code for the logistic DE example**

This appendix can be found in the supplementary materials. It can also be displayed after installing `deBInfer` with the R command:

```
vignette("logistic_ode_example", package="deBInfer")
```

B  **Annotated code for the DDE example**

This appendix can be found in the supplementary materials. It can also be displayed after installing `deBInfer` with the R command:

```
vignette("chytrid_dede_example", package="deBInfer")
```