

## Estimating a Predator-Prey Dynamical Model with the Parameter Cascades Method

Jiguo Cao,<sup>1,\*</sup> Gregor F. Fussmann,<sup>2,\*\*</sup> and James O. Ramsay<sup>3,\*\*\*</sup>

<sup>1</sup>Department of Statistics and Actuarial Science, Simon Fraser University,  
8888 University Drive, Burnaby, British Columbia V5A 1S6, Canada

\**email:* jiguo\_cao@sfu.ca

<sup>2</sup>Department of Biology, McGill University, 1205 Dr. Penfield Avenue,  
Montreal, Quebec H3A 1B1, Canada

\*\**email:* gregor.fussmann@mcgill.ca

<sup>3</sup>Department of Psychology, McGill University, 1205 Dr. Penfield Avenue,  
Montreal, Quebec H3A 1B1, Canada

\*\*\**email:* ramsay@psych.mcgill.ca

**SUMMARY.** Ordinary differential equations (ODEs) are widely used in ecology to describe the dynamical behavior of systems of interacting populations. However, systems of ODEs rarely provide quantitative solutions that are close to real field observations or experimental data because natural systems are subject to environmental and demographic noise and ecologists are often uncertain about the correct parameterization. In this article we introduce “parameter cascades” as an improved method to estimate ODE parameters such that the corresponding ODE solutions fit the real data well. This method is based on the modified penalized smoothing with the penalty defined by ODEs and a generalization of profiled estimation, which leads to fast estimation and good precision for ODE parameters from noisy data. This method is applied to a set of ODEs originally developed to describe an experimental predator–prey system that undergoes oscillatory dynamics. The new parameterization considerably improves the fit of the ODE model to the experimental data sets. At the same time, our method reveals that important structural assumptions that underlie the original ODE model are essentially correct. The mathematical formulations of the two nonlinear interaction terms (functional responses) that link the ODEs in the predator–prey model are validated by estimating the functional responses nonparametrically from the real data. We suggest two major applications of “parameter cascades” to ecological modeling: It can be used to estimate parameters when original data are noisy, missing, or when no reliable priori estimates are available; it can help to validate the structural soundness of the mathematical modeling approach.

**KEY WORDS:** Inverse problem; Nuisance parameters; Ordinary differential equation; Penalized smoothing; Predator–prey system; Profiling method; System identification.

### 1. Introduction

Ecological populations in the field and laboratory frequently display fluctuations in population size that arise due to predator–prey interactions among species (Kendall et al., 1999; Turchin, 2003). Deterministic nonlinear mathematical models, usually in the form of coupled ordinary differential equations (ODEs), display a similar set of dynamical behaviors as experimental data, such as coexistence at an equilibrium, a limit cycle, or a chaotic attractor (e.g., Becks et al., 2005), and are widely used to understand and predict the dynamics of interacting populations. The pioneering and the simplest possible predator–prey dynamic model is the Lotka–Volterra model, which has been modified in many ways since its original formulation in the 1920s (for an overview see Murdoch, Briggs, and Nisbet, 2003). In particular, Rosenzweig and MacArthur (1963) added increased realism to the Lotka–Volterra approach by allowing for density-

dependent growth of the prey population and for nonlinear, saturating uptake of prey by the predator. Today’s models are largely based on the Rosenzweig–MacArthur framework but are typically amended by emphasizing specific factors, such as inducible defenses in the prey (Vos et al., 2004) or adaptive foraging by the predator (Kondoh, 2003).

Although simple, ODE-based modeling approaches satisfactorily describe the general types of dynamics in ecological communities, but they are notoriously difficult to reconcile with the exact quantitative changes in the size of experimental and field populations. This has been attributed to difficulties in correctly parameterizing natural systems of interacting populations and to the fact that these systems are subject to environmental and demographic noise. An alternative explanation would be that the simplifying ODE approach is conceptually and structurally inadequate and, therefore, fails to quantitatively describe community dynamics. In this article

we introduce an improved method to estimate ODE parameters in an experimental predator–prey system. We find that the new parameterization considerably improves the fit of the ODE model to a set of the experimental data. The new method also confirms the structural soundness of the ODE-based modeling approach.

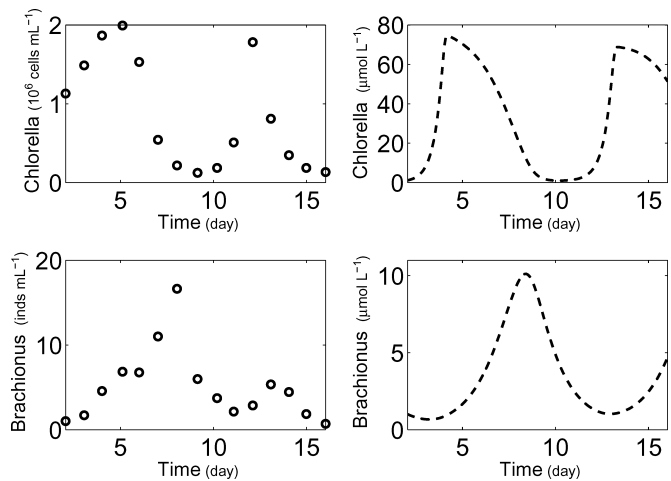
A host of methods have been proposed to estimate ODE parameters from noisy data (see Himmelblau, Jones, and Bischoff, 1967; de Boor and Swartz, 1973; Bock, 1983; Gelman, Bois, and Jiang, 1996; Ellner et al., 1997; Wood, 2001; Ellner, Seifu, and Smith, 2002; and Ionides, Breto, and King, 2006, etc.). Ramsay et al. (2007) developed a new method, which has been shown to solve this problem well by applying penalized smoothing to observations, with the penalty terms defined by ODEs. The smoothing parameters control the trade-off between fitting the data and fidelity to ODEs. In their estimation process, there are three different kinds of parameters. The coefficient vector  $\mathbf{c}$  to the basis function combination is a nuisance parameter because it is essential in the penalized smoothing process, but is not of direct interest. The dimension of  $\mathbf{c}$  also changes with the number of observations and the basis system. The ODE parameter vector  $\boldsymbol{\theta}$  is a structural parameter in the sense of being of primary concern, and the dimension of  $\boldsymbol{\theta}$  is usually fixed and much less than the number of nuisance parameters. The smoothing parameter vector  $\boldsymbol{\lambda}$  is the complexity parameter that decides the effective degrees of freedom of the model. These three kinds of parameters are estimated by three nested optimization levels, which are called the parameter cascades.

We apply this method to an aquatic laboratory community containing two microbial species whose dynamic behavior was studied by Fussmann et al. (2000), Shertzer et al. (2002), and Yoshida et al. (2003). The system is a nutrient-based predator–prey food chain, in which unicellular green algae, *Chlorella vulgaris*, are eaten by planktonic rotifers, *Brachionus calyciflorus*. The growth of *Chlorella* is also limited by the supply of nitrogen. *Chlorella* and *Brachionus* are grown together in replicated, experimental flow-through cultures, called chemostats. Nitrogen continuously flows into the system with the concentration  $N^*$  at the dilution rate  $\delta$ , and all components are removed from the chemostats at the same rate  $\delta$ . According to Fussmann et al. (2000) the system can be mathematically described by a set of nonlinear ODEs, coupled by consumer-resource interactions between the planktonic rotifers, green algae, and the nitrogen resource. Let  $N$ ,  $C$ ,  $R$ ,  $B$  be the concentrations of nitrogen, *Chlorella*, reproducing *Brachionus*, and total *Brachionus*, respectively,  $F_C(N) = b_C N / (k_C + N)$ ,  $F_B(C) = b_B C / (k_B + C)$  be two functional responses (with  $b_C$  and  $b_B$  the maximum birth rates of *Chlorella* and *Brachionus*;  $k_C$  and  $k_B$  the half-saturation constants of *Chlorella* and *Brachionus*), and  $\epsilon$ ,  $\alpha$ , and  $m$  be the assimilation efficiency, the decay of fecundity, and the mortality of *Brachionus*, respectively. The nonlinear ODEs are

$$\begin{aligned} \frac{dN}{dt} &= \delta(N^* - N) - F_C(N)C, \\ \frac{dC}{dt} &= F_C(N)C - F_B(C)B/\epsilon - \delta C, \\ \frac{dR}{dt} &= F_B(C)R - (\delta + m + \alpha)R, \\ \frac{dB}{dt} &= F_B(C)R - (\delta + m)B. \end{aligned} \tag{1}$$

The model includes the mortality and decay of fecundity of *Brachionus* and, contrary to the Rosenzweig–MacArthur approach, treats the mineral resource nitrogen as a separate state variable. This model correctly predicts three qualitative types of dynamic behavior of the experimental system. At low nutrient supply, the predator and prey coexist at an equilibrium (small  $\delta$  or small  $N^*$ ). Increasing  $N^*$  or  $\delta$  switches the system to a limit cycle. Very high nutrient supply leads to extreme oscillations that cause the extinction of the predator or both the predator and the prey. Fussmann et al. (2000) also realized that their model performed rather poorly at predicting quantitative aspects of the experimental predator–prey dynamics. In a series of follow-up studies they found that multiple clones of *Chlorella* coexisted in their experiments, leading to predator-driven cyclical selection among them (Shertzer et al. 2002; Yoshida et al., 2003; Fussmann, Ellner, et al., 2005), which, in turn, provided a biological explanation for the lack of fit between predicted and observed dynamics.

Here we test our method on an experimental data set generated under the same experimental conditions as described in Fussmann et al. (2000), however, with single clone populations of *Chlorella* (see the second figure [a–d] in Yoshida et al. [2003]), which are not subject to the evolutionary dynamics described above. The fact that the concentrations of two state variables (nitrogen and reproducing *Brachionus*) were not measured by Fussmann et al. (2000) poses a challenge. This missing variable problem can also be solved with the parameter cascades method, as discussed in Section 2.1. Figure 1 shows an experimental predator–prey time series at an inflowing nitrogen concentration  $N^* = 80 \mu\text{mol/L}$  and a dilution



**Figure 1.** Example of experimental predator–prey dynamics. The two graphs on the left show the experimental observations for *Chlorella* (algal prey) and *Brachionus* (rotifer predator) at nitrogen concentration (inflow)  $N^* = 80 \mu\text{mol/L}$  and dilution rate  $\delta = 0.68/\text{day}$  (from Yoshida et al. [2003]). The two graphs on the right show the ODE solutions of system (1) with Fussmann et al.’s (2000) parameter values, using the first observations as the initial values. Note the quantitative differences between observed and predicted time series and the necessity to estimate a scaling factor between observed concentrations (in numbers of organisms) and model predictions (all state variables in units of nitrogen).

rate  $\delta = 0.68/\text{day}$ , for which both *Chlorella* and *Brachionus* show oscillatory dynamics. Mathematical simulations of the predator–prey dynamics, using the ODE system and parameterization by Fussmann et al. (2000), result in an unsatisfactory match with the observed population dynamics. We will apply the parameter cascades method to estimate the parameters  $\theta = (\alpha, \epsilon, m, k_B, k_C, b_B, b_C)$  in (1) from the observed data. We exemplify the approach using the data set at  $\delta = 0.68/\text{day}$  and then extend it to three other data sets generated at different dilution rates. The method is further employed to determine the goodness of fit of the ODE model by estimating the functional responses, which are the coupling functions among state variables.

Our article is organized as follows. The method for estimating ODEs from noisy data is introduced in Section 2, Section 3 discusses the effect of the smoothing parameter on the ODE parameter estimates, and parameter estimates from simulated data are conducted in Section 4. Sections 5–7 apply the method to the ecological data set. In Section 5 we estimate the scaling factors between state variables, in Section 6 the functional responses in nonparametric forms, and in Section 7 we derive parameter estimates from the observed data.

## 2. The Parameter Cascades Method

In this section we briefly introduce the parameter cascades method to estimate ODE parameters from the noisy data. These parameter estimates, along with estimated initial values of ODE components, will allow us to solve the ODEs. For simplicity of notation, we first assume that the dynamic system is composed of one single component, and it is straightforward to extend to multiple components. Let  $X(t)$  be a process defined via one ODE  $dX/dt = f(X|\theta)$ , where  $f$  is known. The parameter vector  $\theta$  is unknown and to be estimated with the parameter cascades method from  $n$  observations  $y(t_j) \sim N(X(t_j), \sigma^2)$ . Two nested levels of optimization are implemented. In the first level, we approximate  $X(t)$  with a smooth curve  $x(t)$  by penalized smoothing with the ODE-defined penalty, conditional on the ODE parameter vector  $\theta$ . In this way, the fitted curve  $x(t)$  is a function of  $\theta$ . In the second level, the ODE parameter vector is estimated by minimizing the weighted sum of squared errors (WSSE; WSSE is a function of the fitted curve, and thus is also a function of  $\theta$ ).

### 2.1 Penalized Smoothing with the ODE-Defined Penalty

Let  $\mathbf{y} = (y(t_1), \dots, y(t_n))$  be a vector of  $n$  observations, and the fitted curve  $x(t)$  be a linear expansion of  $K$  basis functions  $\phi_k(t)$ ,  $k = 1, \dots, K$ , as follows:

$$x(t) = \sum_k^K c_k \phi_k(t) = \mathbf{c}'\phi(t).$$

The basis system must have the capacity to approximate ODE solutions, as well as derivatives involved in ODEs. Most ODE solutions have sharp features, such as peaks, valleys, high-frequency oscillations, and discontinuities in derivatives, so we choose the B-spline basis system that can accommodate the discontinuities by assigning multiple knots to the critical locations (Ramsay and Silverman, 2005). In practice, we can explore the ODE solutions under initial esti-

mates of parameters, and decide where we need to put many knots. Or we can begin with a very large number of equally spaced knots, and reduce knot density where appropriate. For instance, the cubic B-spline basis system with 400 equally spaced knots is found appropriate to approximate each component in the predator–prey ODEs, because of the sharp change of the *Chlorella* concentration around the 12th day (Figure 1).

The fitted curve can be obtained by minimizing the sum of squared errors (SSE). To avoid over-fitting, nonparametric smoothing often requires a penalty term to penalize the roughness of the fitted curve. For instance, in order to obtain a smooth fitted curve, the penalty term can be defined in terms of the second derivative, that is,

$$\text{PEN}(x) = \int \left[ \frac{d^2x(t)}{dt} \right]^2 dt.$$

When we require the fitted curve to satisfy an ODE,  $dx(t)/dt = f(x|\theta)$ , it is natural to define the penalty term with the differential operator  $Lx(t) = dx(t)/dt - f(x|\theta)$ :

$$\text{PEN}(x|\theta) = \int [Lx(t)]^2 dt, \tag{2}$$

and the fitting criterion to estimate the smooth curve is given by

$$J(\mathbf{c}|\theta, \lambda, \mathbf{y}) = \sum_{i=1}^n [y(t_i) - x(t_i)]^2 + \lambda \int [Lx(t)]^2 dt. \tag{3}$$

Suppose there are  $S$  ODEs and  $T$  components, with only  $M \leq T$  of these components observed. Then the fitting criterion can be generalized to be

$$\begin{aligned} H(\mathbf{c}|\theta, \lambda, \mathbf{y}) &= \sum_{j=1}^M \text{SSE}_j + \sum_{d=1}^S \lambda_d \text{PEN}_d \\ &= \sum_{j=1}^M \omega_j \sum_{i=1}^{n_j} [y_j(t_{ij}) - x_j(t_{ij})]^2 \\ &\quad + \sum_{\ell=1}^S \lambda_\ell \omega_\ell \int [L_\ell \mathbf{x}(t)]^2 dt, \end{aligned} \tag{4}$$

where  $y_j(t_{ij})$  is the observation for  $j$ th component at  $t_{ij}$ , and  $\mathbf{x}(t) = (x_1(t), \dots, x_T(t))$  is a vector of fitted curves for the total  $T$  components.  $T$  is often larger than  $M$ , which means there are some unobservable components. For instance, in our predator–prey ODEs (1), only the concentrations of *Chlorella* ( $C$ ) and total *Brachionus* ( $B$ ) are observed, and we have  $S = T = 4$  and  $M = 2$ . When some components are not observed, the corresponding smooth curves for these missing components are estimated by forcing them to minimize the ODE-defined penalty term because these missing components are involved in the ODEs. The differential operator  $L_\ell \mathbf{x}(t) = dx_\ell(t)/dt - f_\ell(\mathbf{x}|\theta)$  is defined by the  $\ell$ th ODE:  $dx_\ell(t)/dt = f_\ell(\mathbf{x}|\theta)$ . Parameter  $\omega_j$  is the normalizing weight, which is required in order to keep different components having comparable scales for  $\text{SSE}_j$  and  $\text{PEN}_j$ . Ramsay et al. (2007) gave several strategies for the choice of  $\omega_j$ . The smoothing parameter  $\lambda_\ell$  controls the trade-off between fitting to data and

fidelity to ODEs. When  $L$  is a nonlinear differential operator, the penalty term  $\text{PEN}_d$  can be approximated by the numerical quadrature (Ramsay et al., 2007).

2.2 Statistical Inference for the ODE Parameter Vector  $\theta$

Conditional on  $\theta$ , the coefficient vector  $c$  can be estimated by minimizing the criterion  $J(c|\theta, \lambda, y)$  in (4). In other words, the estimate  $\hat{c}$  can be treated as a function of the ODE parameter vector  $\theta$ . This function  $\hat{c}(\theta)$  is explicit if the ODEs are linear. When the ODEs are nonlinear, the function  $\hat{c}(\theta)$  is implicit and its derivatives can be estimated using the implicit function theorem.

The parameter vector  $\theta$  can be estimated by optimizing the criterion  $H(\theta|\lambda, y)$  defined by

$$H(\theta|\lambda, y) = \sum_{j=1}^M \omega_j \sum_{i=1}^n [y_j(t_i) - \hat{x}_j(t_i|\theta)]^2. \tag{5}$$

Note that  $\hat{x}_j(t|\theta) = \hat{c}_j(\theta)' \phi_j(t)$  is a function of  $\theta$  by considering the functional relationship between  $\hat{c}$  and  $\theta$ . The two nested optimization levels can be implemented quickly via Newton–Raphson-type method by working out the gradients and Hessian matrices analytically, as shown by Ramsay et al. (2007).

Let  $\Sigma$  be the variance–covariance matrix for the data  $y$ ; Ramsay et al. (2007) show that the variance for the estimate  $\hat{\theta}$  can be estimated with a modified  $\delta$ -method:

$$\text{var}(\hat{\theta}) = \left[ \frac{d\hat{\theta}}{dy} \right] \Sigma \left[ \frac{d\hat{\theta}}{dy} \right]',$$

where  $d\hat{\theta}/dy$  can be derived with the implicit function theorem

$$\frac{d\hat{\theta}}{dy} = - \left[ \frac{d^2 H}{d\theta^2} \Big|_{\hat{\theta}} \right]^{-1} \left[ \frac{d^2 H}{d\theta dy} \Big|_{\hat{\theta}} \right],$$

where

$$\frac{d^2 H}{d\theta^2} = \frac{\partial^2 H}{\partial \theta^2} + 2 \frac{\partial^2 H}{\partial \hat{c} \partial \theta} \frac{\partial \hat{c}}{\partial \theta} + \left( \frac{\partial \hat{c}}{\partial \theta} \right)' \frac{\partial^2 H}{\partial \hat{c}^2} \frac{\partial \hat{c}}{\partial \theta} + \frac{\partial H}{\partial \hat{c}} \frac{\partial^2 \hat{c}}{\partial \theta^2}, \tag{6}$$

and

$$\begin{aligned} \frac{d^2 H}{d\theta dy} &= \frac{\partial^2 H}{\partial \theta \partial y} + \left[ \frac{\partial \hat{c}}{\partial \theta} \right]' \frac{\partial^2 H}{\partial \hat{c} \partial y} + \frac{\partial^2 H}{\partial \theta \partial \hat{c}} \frac{\partial \hat{c}}{\partial y} \\ &+ \left[ \frac{\partial \hat{c}}{\partial \theta} \right]' \frac{\partial^2 H}{\partial \hat{c}^2} \frac{\partial \hat{c}}{\partial y} + \frac{\partial H}{\partial \hat{c}} \frac{\partial^2 \hat{c}}{\partial \theta \partial y}. \end{aligned} \tag{7}$$

More details for formulas (6) and (7) can be found in Ramsay et al. (2007).

2.3 Estimating Initial Values of Components in ODEs

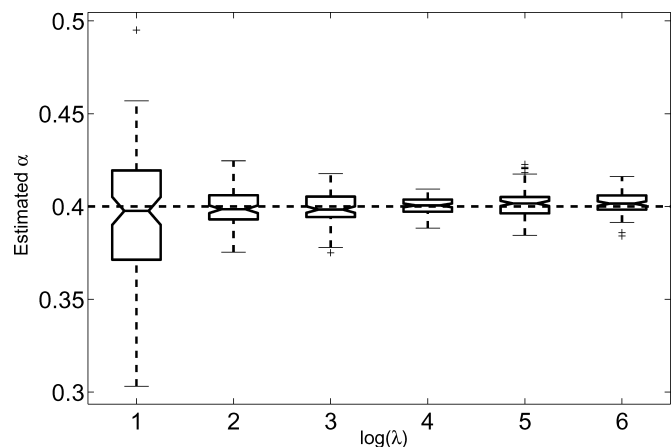
Numerically solving ODEs requires initial values, which are the values of ODE components at the first time point. A small change in initial values may result in a large difference in the numerical ODE solutions. However, observations in real life, including the observed initial values, usually have some measurement errors, and it is dangerous to use the first observations as the initial values directly. Moreover, some components in ODEs are not observable, in which case there is no way to observe the initial values for these components.

The byproduct of the parameter cascades method is that the fitted curves for all components can be obtained after we derive the ODE parameter estimate  $\hat{\beta}$ . We can then estimate initial values by evaluating the fitted curves for all components at the first time point. These ODE parameter estimates and initial value estimates can then be used to solve the ODEs.

3. Effect of the Smoothing Parameter  $\lambda$

The smoothing parameter  $\lambda$  controls the trade-off between fitting to data and fidelity to ODEs in the inner criterion (4), which implicitly controls the functional relationship between the coefficient vector estimate  $\hat{c}$  and the ODE parameter vector  $\theta$ . So the smoothing parameter has a large effect on the ODE parameter estimates. In the following, we explore the smoothing parameter effect on ODE parameter estimates with simulation.

Each simulated data set is generated by adding Gaussian noise to the predator–prey ODE solutions at the equal-spaced time points in  $[0, 30]$  with the step 0.1. The predator–prey ODEs are solved based on parameter values provided in Fussmann et al. (2000). Here we explore the smoothing parameter effect based on dense simulated data in order to exclude the sparseness effect of simulated data. We fix parameters  $k_C, k_B, b_C,$  and  $b_B,$  and estimate the other parameters  $\epsilon, \alpha,$  and  $m$  from 100 such simulated data sets when the smoothing parameter  $\lambda$  ranges from 10 to  $10^6$ . Each component is approximated by a cubic B-spline basis system generated by putting one knot on each time point with observations. The boxplot for estimates of  $\alpha$  is shown in Figure 2. The estimates for  $\alpha$  are almost unbiased, independent of the values of the smoothing parameter  $\lambda$ . On the other hand, a small smoothing parameter



**Figure 2.** Boxplots of multiple estimates of the parameter  $\alpha$  in the predator–prey ODEs for different values of the smoothing parameter  $\lambda$ . Plots are based on 100 simulated data sets, which are generated by adding Gaussian noise with  $STD_C = 3, STD_B = 0.3$  to predator–prey ODE solutions for *Chlorella* and *Brachionus* at the equally spaced time points in  $[0, 30]$  with the step 0.1. Each variable is approximated by cubic B-splines generated with one knot on each observation. The dashed line in the boxplot is the true value of the parameter. Parameter units are omitted.

value, such as 10, leads to a large variance of estimated  $\alpha$ 's. Estimates of  $\epsilon$  and  $m$  display the same properties as estimates of  $\alpha$ . In the rest of this article, the value of the smoothing parameter is chosen as  $10^4$ , which results in the smallest bias and variance of parameter estimates.

#### 4. Parameter Estimates from Simulated Data

We perform simulations to explore the statistical identifiability of the ODE parameters and to verify the ODE parameter estimates with the parameter cascades method. We estimate the parameter vector  $\theta = (\epsilon, \alpha, m, b_C, b_B, k_C, k_B)$  in (1) on 100 simulated data sets. The simulated data are generated by adding Gaussian noise with  $STD_C = 3$ ,  $STD_B = 0.3$  to the predator–prey ODE solutions for *Chlorella* and *Brachionus*, respectively, with two observations per day in  $[0, 16]$ . The predator–prey ODEs are solved based on parameter values provided in Fussmann et al. (2000). Here we simulate data sets that have the similar sparseness as the real data sets in order to test whether our method can work in these sparse data sets. The scale of noise is selected such that coefficients of variance of simulated data for *Chlorella* and *Brachionus* are about the same. Each variable is approximated by the cubic B-spline with 200 equal-spaced knots in  $[0, 16]$ . The weights  $\omega_j$ ,  $j = 1, 2, 3, 4$  in (4) are chosen as the reciprocals of variances of the predator–prey ODE solutions, which are 0.0013, 0.0015, 0.18, 0.099, respectively. The smoothing parameter  $\lambda_\ell = 10^4$ ,  $\ell = 1, 2, 3, 4$ . A summary for parameter estimates is given in Table 1, where the true parameter values fall into the 95% experimental confidence intervals. The small values of standard deviations for the ODE parameter estimates confirm the statistical identifiability of the ODE parameters.

#### 5. Rescaling the Observed Data

Inspection of the y-axes in Figure 1 reveals large differences in scale between observed data and ODE solutions based on parameter values in Fussmann et al. (2000), because the units of data collected from the experimental system differ from those used in the ODE model. Algae take up nitrogen from the medium and rotifers take up algae, so both algae and rotifers contain nitrogen. The ODE model uses molar concentrations of nitrogen in the base medium for all state variables. That is, the ODE solutions for algae and rotifers reflect the molar concentrations of nitrogen contained in their respective populations per unit of liquid medium. Experimental data

of population size, however, reflect counts of individuals per unit of liquid medium. Thus, for this particular data set we rescale the observed data before fitting ODEs. The two rescaling factors are the average molar concentrations of nitrogen per individual of *Chlorella* or *Brachionus*. However, for other cases where we can obtain these rescaling parameters theoretically based on the biological knowledge, we do not recommend to estimate them statistically. Let  $\mathbf{y}_j = (y_j(t_1), \dots, y_j(t_{n_j}))$  be the functional data for the variable  $y_j(t)$ , and  $x_j(t)$  be the corresponding ODE solution obtained from some numerical methods, then we can rescale data  $\mathbf{y}_j$  with a constant coefficient  $s_j$  by minimizing

$$H(s_j | \mathbf{y}_j) = \sum_{i=1}^{n_j} (s_j y_j(t_i) - x_j(t_i))^2. \tag{8}$$

It is easy to derive that

$$s_j = \frac{\sum_{i=1}^{n_j} [x_j(t_i) y_j(t_i)]}{\sum_{i=1}^{n_j} [y_j(t_i)]^2}. \tag{9}$$

The estimated scale parameters are 28 and 0.57 for *Chlorella* and *Brachionus*, respectively, when we rescale observations to the ODE solutions with the parameter values obtained from Fussmann et al. (2000), using the first observations as initial values. Allowing for the differences in volume in the composed units (per L vs. per mL), these two scale parameters can be interpreted as follows: the amount of nitrogen contained in  $10^6$  *Chlorella* cells is 28 nmol and one individual of *Brachionus* contains 0.57 nmol. The rescaled data are shown in Figure 3. Although observed and predicted data are now at comparable scale, the rescaled *Chlorella* data are still far from the ODE solutions for *Chlorella*, especially at the boundaries of the observation period. The ODE solutions for *Brachionus* clearly fail to match the period length of the oscillatory dynamics.

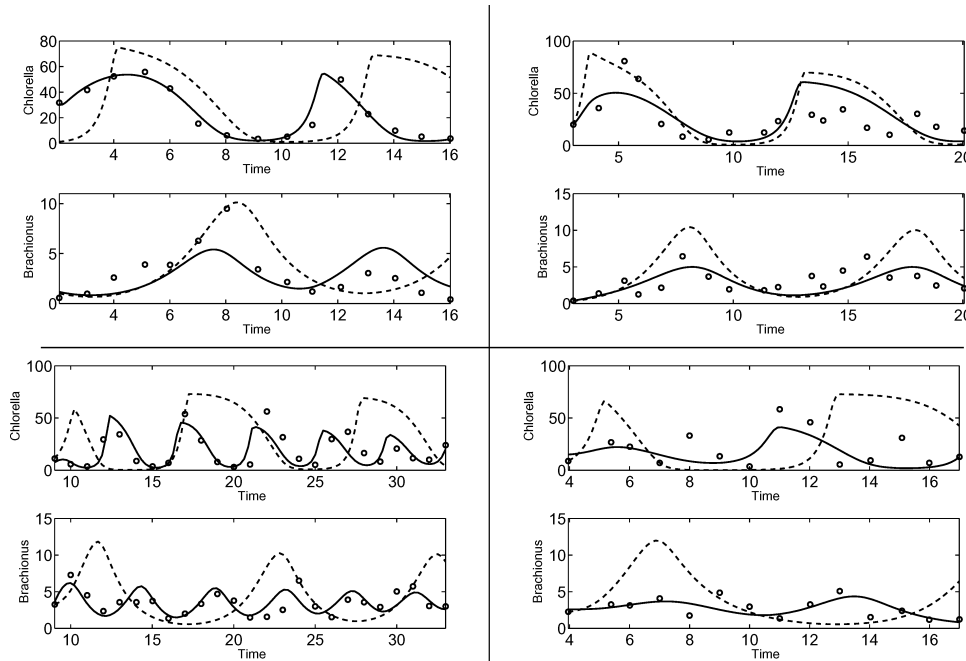
#### 6. Estimating Functional Responses in ODEs from Observed Data

Parameter value optimization can improve the match between simulated and observed data in systems described by ODEs

**Table 1**

*Parameter estimates on 100 simulated data sets. The simulated data are generated by adding Gaussian noise with  $STD_C = 3$ ,  $STD_B = 0.3$  to the ODE solutions for *Chlorella* and *Brachionus*, respectively, with two observations per day in  $[0, 16]$ . Each variable is approximated by cubic B-spline with 200 equal-spaced knots in  $[0, 16]$ . The smoothing parameter  $\lambda = 10^4$ . Parameter units are omitted.*

Parameters	$\epsilon$	$\alpha$	$m$	$b_C$	$b_B$	$k_C$	$k_B$
True	0.25	0.4	0.055	3.3	2.25	4.3	15
Lower 95% bound	0.24	0.37	0.013	3.13	2.19	3.84	14.6
Upper 95% bound	0.27	0.45	0.101	3.5	2.33	5.15	15.4
BIAS (* $10^{-2}$ )	0.29	0.84	0.18	0.023	1.07	19.7	0.92
STD (* $10^{-2}$ )	0.74	2.1	2.2	8.7	3.6	33	21



**Figure 3.** Solutions of the predator-prey ODEs (1) with parameter and initial values optimized by the parameter cascades method (solid lines). Observed experimental data are from Yoshida et al. (2003; Figure 2 a–d), with dilution rates  $\delta = 0.68/\text{day}$  (the top left two graphs),  $\delta = 0.67/\text{day}$  (the top right two graphs),  $\delta = 0.65/\text{day}$  (the bottom left two graphs), and  $\delta = 0.57/\text{day}$  (the bottom right two graphs). Each component is approximated by order 4 B-splines with 400 equal-spaced knots. The smoothing parameter is  $\lambda = 10^4$ . The dashed lines are the ODE solutions with the parameter values obtained from Fussmann et al. (2000), using the first observations as initial values. The circles are the rescaled observations, with the scale parameters estimated by rescaling the original data to fit the dashed lines. The unit of *Chlorella* and *Brachionus* is  $\mu\text{mol/L}$ , and the unit of time is day.

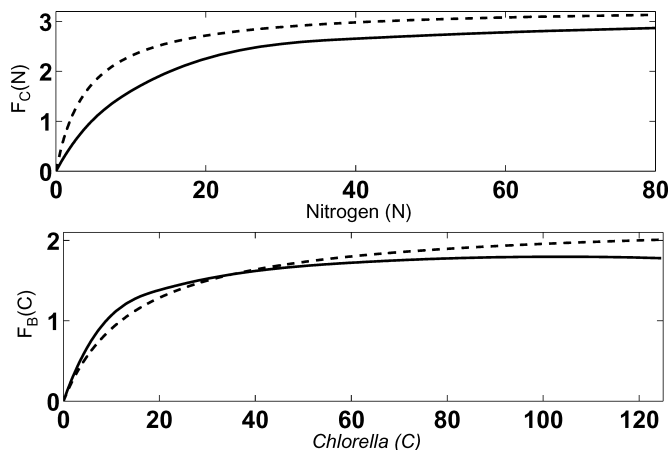
but this method is applied within the limits of the structural soundness of the mathematical model. By structural soundness we mean the fact that the mathematical model adequately reflects the mechanisms that influence the dynamics of the real (in our case, biological) system. Of particular importance are functions that link several state variables by describing the general type of interaction that exists between them. For example, in the predator-prey ODEs (1), the so-called functional responses  $F_C(N) = b_C N / (k_C + N)$  and  $F_B(C) = b_B C / (k_B + C)$  describe the effect of nitrogen concentration on the rate of change of the *Chlorella* concentration, and the effect of the *Chlorella* concentration on the rate of change of the *Brachionus* concentration, respectively. The preceding mathematical formulation of the predator-prey interaction as a nonlinear, saturating uptake function is standard in ecological modeling, but different uptake dynamics are frequently observed in natural systems (e.g., sigmoid functions), and have been shown to greatly affect the dynamics of ecological multispecies models (Williams and Martinez, 2004; Fussmann and Blasius, 2005). In the following, we estimate the functional responses nonparametrically from the rescaled observed data. The two functional responses are expressed as linear combinations of B-spline basis functions, which can be written as

$$F_C(N) = \sum (c_i^1 \psi_i^1(N)), \tag{10}$$

$$F_B(C) = \sum (c_i^2 \psi_i^2(C)), \tag{11}$$

where  $\psi_i^1(N)$  and  $\psi_i^2(C)$  are basis functions, and  $c_i^1$  and  $c_i^2$  are the corresponding coefficients, respectively. The functional response  $F_C(N)$  is expanded by the cubic B-spline basis with interior knots 10 and 40, and the functional response  $F_B(C)$  is expanded by the cubic B-spline basis with interior knots 20 and 60. The smoothing parameter  $\lambda = 10^4$ . We approximate variables in the predator-prey ODEs (1) by the cubic B-spline basis with 400 equally spaced knots. We choose the above basis functions for the two functional responses and variables because they lead to good estimates on the simulated data.

We estimate the two functional responses from the rescaled observed data. The coefficients  $c_i^1$  and  $c_i^2$ , along with  $\epsilon$ ,  $m$ , and  $\alpha$ , are treated as the ODE parameters, which are estimated in the second level of the parameter cascade method. Figure 4 displays the estimated functional responses for  $F_C(N)$  and  $F_B(C)$ , which have the same general shape as the functional responses in (1) but show some differences in steepness and saturation level of the response. These differences are due to different parameter values in the functional response but the forms of functional responses proposed by Fussmann et al. (2000) are verified to be appropriate. In the next section we will estimate all parameters in (1) from the rescaled observed data.



**Figure 4.** The estimated nonparametric functional responses for  $F_C(N)$  (top) and  $F_B(C)$  (bottom) have the same patterns as the functional responses proposed by Fussmann et al. (2000). The solid lines are the estimated nonparametric functional responses. The dashed lines are the Fussmann’s functional responses  $F_C(N) = b_C N / (k_C + N)$ , and  $F_B(C) = b_B C / (k_B + C)$ . The functional response  $F_C(N)$  is expanded by the cubic B-spline basis with interior knots 10 and 40 and the functional response  $F_B(C)$  is expanded by the cubic B-spline basis with interior knots 20 and 60. We approximate variables in the predator-prey ODEs (1) by the cubic B-spline basis with 400 equally spaced knots. The smoothing parameter  $\lambda = 10^4$ . The unit of nitrogen and *Chlorella* is  $\mu\text{mol/L}$ .

**7 Parameter Estimation from Observed Data**

We estimate the ODE parameter vector  $\theta = (\alpha, \epsilon, m, k_B, k_C, b_B, b_C)$  from the rescaled observed data set with the dilution rate  $\delta = 0.68/\text{day}$ . Each component is expanded by the cubic B-spline with 400 equally spaced knots. The weights  $\omega_j, j = 1, 2, 3, 4$  in (4) are chosen as the reciprocals of variances of the predator-prey ODE solutions, which are 0.0011, 0.0011, 0.16,

0.094, respectively, such that the normalized sums of squared errors are of roughly comparable sizes. The smoothing parameter  $\lambda_\ell = 10^4, \ell = 1, 2, 3, 4$ . The parameter estimates from the rescaled observed data are shown in Table 2, and the mean squared errors (MSEs) between data and ODE solutions with our parameter estimates have a fivefold decrease. The standard errors (SEs) for ODE parameter estimates are calculated with the modified  $\delta$ -method (Section 2.2). Figure 3 (upper left) displays the solutions of the predator-prey ODEs (1) with our parameter estimates, using the estimated initial values. The ODE solution for *Chlorella* fits the data very well over the whole observation period. The same is true for the rescaled *Brachionus* data, except for day 8, which we suspect to be an outlier.

We also performed the same analysis on the other three data sets (experiments conducted at different dilution rates), and the results are shown in Table 2 and Figure 3. The parameter estimates from these data sets are different, but the MSEs between data and ODE solutions with the parameter estimates are all greatly decreased. We also notice that some parameter values are well defined by the data, as indicated by their small SEs, and others are poorly identified, such as parameters  $\alpha, m, k_C$ , and  $k_B$ . This suggests we might simplify the model by fixing poorly defined parameter values at reasonable values.

**8. Conclusion and Discussion**

ODEs have been widely utilized in engineering, biology, medicine, economics, and a host of other areas. We apply the parameter cascades method to estimate parameters in a set of predator-prey ODEs from experimental data. The initial values for ODE variables can be estimated directly by evaluating the fitted curves at the first time point. We have shown that the ODE solutions with our estimated parameter values and initial values can fit four different experimental data sets well, although we miss observations for two out of four variables in the ODEs. We also estimate nonparametrically two functional responses in the predator-prey ODEs, and validate

**Table 2**

Parameter estimates and the standard errors (SEs) for the predator-prey ODEs (1) from the rescaled observed data sets, which are collected by changing the dilution rate  $\delta$ . Each component is approximated by order 4 B-splines with 400 equal-spaced knots.

The smoothing parameter  $\lambda = 10^4$ . MSE is the mean squared errors of the observations to the ODE solutions with our parameters and initial values estimates. As a comparison, we also give the parameter estimates given in Fussmann et al. (2000).

Parameter units are omitted.

Data sets	Estimates	$\epsilon$	$\alpha$	$m$	$b_C$	$b_B$	$k_C$	$k_B$	MSE
$\delta = 0.68$	Fussmann	0.25	0.40	0.055	3.3	2.25	4.3	15.0	1.96
	Profiling	0.11	0.01	0.152	3.9	1.97	4.3	15.7	0.34
	SEs	0.020	0.14	0.073	0.47	0.26	1.95	2.01	
$\delta = 0.67$	Fussmann	0.25	0.40	0.055	3.3	2.25	4.3	15.0	2.56
	Profiling	0.15	0.50	1e-5	3.0	2.09	4.5	15.3	0.88
	SEs	0.013	0.11	0.014	0.12	0.11	1.5	1.4	
$\delta = 0.65$	Fussmann	0.25	0.40	0.055	3.3	2.25	4.3	15.0	5.50
	Profiling	0.20	0.80	0.52	5.6	3.75	4.8	12.3	0.53
	SEs	0.011	0.057	0.041	0.11	0.13	0.18	0.70	
$\delta = 0.57$	Fussmann	0.25	0.40	0.055	3.3	2.25	4.3	15.0	6.64
	Profiling	0.16	0.80	0.095	3.3	2.81	3.8	14.0	0.67
	SEs	0.027	0.30	0.079	0.15	0.37	1.43	0.77	

the originally proposed nonlinear forms for the two functional responses. The smoothing parameter controls the trade-off between fitting to the data and fidelity to ODEs. We have shown with simulation that small values of the smoothing parameter result in large variances of parameter estimates.

Many methods for estimating ODEs have to solve ODEs numerically when searching for optimized ODE parameter values, which is computationally expensive and requires knowing the initial values of ODE variables. On the other hand, the parameter cascades method approximates ODE solutions nonparametrically, which reduces computation load dramatically. The gradients and Hessian matrices are also worked out analytically, so the optimization process is fast and stable. A modified Delta method is developed to estimate the standard errors of the ODE parameter estimates, and these variances take the uncertainty coming from the estimates for the spline coefficients and the smoothing parameters into account (Cao and Ramsay, 2007). The variance estimates for ODE parameters can further indicate the identifiability for ODE parameters. Nevertheless, it is always a good idea to implement simulation to verify the identifiability for ODE parameters. We also suggest to vary the initial values when searching for optimal ODE parameter values to make sure that they converge to the global optimum. A user-friendly program has been developed to implement this method and is available from the website <http://www.functionaldata.org>.

Our analysis of the experimental data with the parameter cascades method has several implications for the biological interpretation of these data. The method reveals that the original parameter values provided by Fussmann et al. (2000) are a suboptimal set of estimates. This is not a very surprising finding, given the large number of parameters involved in this predator-prey system and the difficulty of measuring all of them reliably in a live system. It seems almost unavoidable that an empirical parameterization can be improved by a statistical method that seeks to optimize parameter values on the basis of time-series data. This is not to say that the improved parameterization we found is “right” in an absolute sense and should take precedent over the empirical one. This can be immediately understood when looking at the estimates we obtain for each of the parameters from four different experimental trials (Table 2). Some parameter estimates are quite different among the four trials although they all describe the same predator-prey system (the only difference is the dilution rate at which the experiments are run). Obviously, there is no universally “best” parameterization for the predator-prey system. However, the parameter cascades method helps us to identify empirical parameter values that are consistently “off” (e.g., the parameter  $\epsilon$ , for which a lower parameter value than the empirical 0.25 resulted in a better fit in all four trials) and to distinguish them from parameters for which empirical and profiling estimate are in good agreement (e.g., the half-saturation constants  $k_C$  and  $k_B$  of the functional responses). Consequently, we have higher confidence in those estimates for which empirical and statistical estimates agree. In practice, it might also be advisable to weight or constrain parameter estimates before subjecting them to the cascades method. For instance, the birth rate estimate of 5.6/day for *Chlorella* (Table 2;  $\delta = 0.65$ ) is physiologically impossible. Although constraining this parameter (and others for which

natural limits exist) would result in a reduced goodness of fit, the realism of the model would increase.

Although the parameter cascades method reveals deficiencies in the parameterization of the predator-prey model, it corroborates its general structural correctness with regard to the linking functions between the state variables (the “functional responses”). This is encouraging because ecological modeling necessarily relies on simplifying assumptions about the mechanism that are at work in natural communities. There is a longstanding debate in ecology about the correct form of the functional response in dynamical systems (e.g., Hassell, Lawton, and Beddington, 1977; Jost and Ellner, 2000; Fussmann Weithoff, and Yoshida, 2005; Jensen, Jeschke, and Ginzburg, 2007). Our results gave us no reason to reject the most widely used model in predator-prey dynamics: a monotonously increasing but saturating function of prey concentration (Holling, 1959; Ivlev, 1961).

In conclusion, the parameter cascades method is proved to be a useful mathematical method for analyzing dynamic ODE models in ecology and other fields. It can be used to estimate parameters when original data are noisy, missing, or when no reliable a priori estimates are available, and it can help to validate the structural soundness of the mathematical modeling approach.

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#### REFERENCES

- Becks, L., Hilker, F. M., Malchow, H., Jürgens, K., and Arndt, H. (2005). Experimental demonstration of chaos in a microbial food web. *Nature* **435**, 1226.
- Bock, H. G. (1983). Recent advances in parameter identification techniques for ordinary differential equations. In *Numerical Treatment of Inverse Problems in Differential and Integral Equations*, P. Deuffhard and E. Harrier (eds), 95–121. Basel, Switzerland: Birkhäuser.
- Cao, J. and Ramsay, J. O. (2007). Parameter cascades and profiling in functional data analysis. *Computational Statistics* **22**, 335–351.
- de Boor, C. and Swartz, B. (1973). Collocation at Gaussian points. *SIAM Journal on Numerical Analysis* **10**, 582–606.
- Ellner, S. P., Kendall, B. E., Wood, S. N., McCauley, E., and Briggs, C. J. (1997). Inferring mechanism from time-series data: Delay-differential equations. *Physics D* **110**, 182–194.
- Ellner, S. P., Seifu, Y., and Smith, R. H. (2002). Fitting population dynamic models to time-series data by gradient matching. *Ecology* **83**, 2256–2270.
- Fussmann, G. F. and Blasius, B. (2005). Community response to enrichment is highly sensitive to model structure. *Biology Letters* **1**, 9–12.



- Fussmann, G. F., Ellner, S. P., Shertzer, K. W., and Hairston, N. G. J. (2000). Crossing the Hopf bifurcation in a live predator-prey system. *Science* **290**, 1358–1360.
- Fussmann, G. F., Ellner, S. P., Hairston, N. G., Jones, L. E., Shertzer, K. W., and Yoshida, T. (2005). Ecological and evolutionary dynamics of experimental plankton communities. *Advances in Ecological Research* **37**, 221–243.
- Fussmann, G. F., Weithoff, G., and Yoshida, T. (2005). A direct, experimental test of resource vs. consumer dependence. *Ecology* **86**, 2924–2930.
- Gelman, A., Bois, F., and Jiang, J. (1996). Physiological pharmacokinetic analysis using population modeling and informative prior distributions. *Journal of the American Statistical Association* **91**, 1400–1412.
- Hassell, M. P., Lawton, J. H., and Beddington, J. R. (1977). Sigmoid functional responses by invertebrate predators and parasitoids. *Journal of Animal Ecology* **46**, 249–262.
- Himmelblau, D., Jones, C., and Bischoff, K. B. (1967). Determination of rate constants for complex kinetics models. *Industrial Engineering Chemistry Fundamentals* **6**, 539.
- Holling, C. S. (1959). The components of predation as revealed by a study of small-mammal predation of the European pine sawfly. *The Canadian Entomologist* **91**, 293–320.
- Ionides, E. L., Breto, C., and King, A. A. (2006). Inference for nonlinear dynamical systems. *Proceedings of the National Academy of Sciences* **103**, 18438–18443.
- Ivlev, V. S. (1961). *Experimental Ecology of the Feeding of Fishes*. New Haven, CT: Yale University Press.
- Jensen, C. X. J., Jeschke, J. M., and Ginzburg, L. R. (2007). A direct, experimental test of resource vs. consumer dependence: Comment. *Ecology* **88**, 1600–1602.
- Jost, C. and Ellner, S. P. (2000). Testing for predator dependence in predator-prey dynamics: A non-parametric approach. *Proceedings of the Royal Society of London, Series B—Biological Sciences* **267**, 1611–1620.
- Kendall, B. E., Briggs, C. J., Murdoch, W. W., Turchin, P., Ellner, S. P., McCauley, E., Nisbet, R. M., and Wood, S. N. (1999). Why do populations cycle? A synthesis of statistical and mechanistic modeling approaches. *Ecology* **80**, 1789–1805.
- Kondoh, M. (2003). Foraging adaptation and the relationship between food-web complexity and stability. *Science* **299**, 1388–1391.
- Murdoch, W., Briggs, C., and Nisbet, R. (2003). *Consumer-Resource Dynamics*. New York: Princeton University Press.
- Ramsay, J. O. and Silverman, B. W. (2005). *Functional Data Analysis*, 2nd ed. New York: Springer.
- Ramsay, J. O., Hooker, G., Campbell, D., and Cao, J. (2007). Parameter estimation for differential equations: A generalized smoothing approach (with discussion). *Journal of the Royal Statistical Society, Series B* **69**, 741–746.
- Rosenzweig, M. L. and MacArthur, R. H. (1963). Graphical representation and stability conditions of predator-prey interactions. *American Naturalist* **97**, 209.
- Shertzer, K. W., Ellner, S. P., Fussmann, G. F., and Hairston, N. G. (2002). Predator-prey cycles in an aquatic microcosm: Testing hypotheses of mechanism. *Journal of Animal Ecology* **71**, 802–815.
- Turchin, P. (2003). *Complex Population Dynamics*. Princeton, NJ: Princeton University Press.
- Vos, M., Kooi, B. W., DeAngelis, D. L., and Mooij, W. M. (2004). Inducible defences and the paradox of enrichment. *Oikos* **105**, 471–480.
- Williams, R. J. and Martinez, N. D. (2004). Stabilization of chaotic and non-permanent food-web dynamics. *European Physical Journal B* **38**, 297–303.
- Wood, S. N. (2001). Partially specified ecological models. *Ecological Monographs* **71**, 1–25.
- Yoshida, T., Jones, L. E., Ellner, S. P., Fussmann, G. F., and Hairston, N. G. (2003). Rapid evolution drives ecological dynamics in a predator-prey system. *Nature* **424**, 303–306.

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