Journal of Theoretical Biology 283 (2011) 82–91

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Structural sensitivity of biological models revisited

Cordoleani Flora [a,*], Nerini David [a], Gauduchon Mathias [a], Morozov Andrew [b], Poggiale Jean-Christophe [a]

[a] Centre d'Oceanologie de Marseille (COM), Université de la Méditerranée, UMR LMGEM 6117 CNRS, Campus de Luminy, Case 901, 13288 Marseille Cedex 09, France
[b] Department of Mathematics, University of Leicester, University Road, Leicester LE1 7RH, United Kingdom

ARTICLE INFO

Article history:
Received 9 March 2011
Received in revised form
11 May 2011
Accepted 16 May 2011
Available online 30 May 2011

Keywords:
System stability
Hausdorff distance
Data variability
Functional response
Chemostat model

ABSTRACT

Enhancing the predictive power of models in biology is a challenging issue. Among the major difficulties impeding model development and implementation are the sensitivity of outcomes to variations in model parameters, the problem of choosing of particular expressions for the parametrization of functional relations, and difficulties in validating models using laboratory data and/or field observations. In this paper, we revisit the phenomenon which is referred to as structural sensitivity of a model. Structural sensitivity arises as a result of the interplay between sensitivity of model outcomes to variations in parameters and sensitivity to the choice of model functions, and this can be somewhat of a bottleneck in improving the models predictive power. We provide a rigorous definition of structural sensitivity and we show how we can quantify the degree of sensitivity of a model based on the Hausdorff distance concept. We propose a simple semi-analytical test of structural sensitivity in an ODE modeling framework. Furthermore, we emphasize the importance of directly linking the variability of field/experimental data and model predictions, and we demonstrate a way of assessing the robustness of modeling predictions with respect to data sampling variability. As an insightful illustrative example, we test our sensitivity analysis methods on a chemostat predator–prey model, where we use laboratory data on the feeding of protozoa to parameterize the predator functional response.

1. Introduction

Improving the predictive power of biological models is a challenging issue. The current tendency in the literature is toward the increasing of model complexity with the aim of incorporating more and more "realistic" features, which often translates itself into including more variables and model parameters. As an example, in marine ecology models have evolved from simple mean-field NPZ systems to complex spatial systems involving a large number of variables (see Carlotti and Poggiale, 2010 for a review of food web marine plankton models). However, such an increase in model complexity does not always signify more predictive power (Arhonditsis and Brett, 2004; Fulton et al., 2004). A central question concerns the choice of the necessary details to be included into the model in order to attain a compromise between the realism of the process modeled and the tractability of the mathematical construction (Demongeot et al., 2009). Note that one of the major difficulties impeding efficient model-based predictions is a large degree of uncertainty regarding the processes involved. Partially, this can be overcome by using more sophisticated experimental devices and more extensive collection of field data.

The use of experimental/observational data in the validation of models can be tricky. For example, experimental data are often obtained on a small (laboratory) spatial scale and under particularly specific conditions, and as a result, in the case where a model is validated based on laboratory experiments, implementation of the modeling predictions in the natural environment on larger temporal and spatial scales can be erroneous (Poggiale, 1998; Begon et al., 2002; Englund and Leonardsson, 2008; Morozov and Arashkevich, 2010; Morozov, 2010). Various reasons can be the cause of these discrepancies: spatial heterogeneity, temporal variability, behavioral complexities of species, environmental noise and many others. This problem is even more critical when concerning models designed for long term predictions, in which a variable environment creates a new gap between the conditions of well controlled experiments and the real world.

Another crucial factor when constructing a model is deciding which parametrization (i.e. the choice of a particular function) to use to describe a certain ecological process. Different approaches exist in ecological literature to cope with the lack of information about the particular functions which we need to implement in equations. For example, one can consider a model without explicitly specifying the functions, we only require that those functions satisfy certain

* Corresponding author. Tel.: +33 4 91 82 91 26; fax: +33 4 91 82 96 41.
E-mail addresses: flora.cordoleani@univmed.fr (C. Flora), david.nerini@univmed.fr (N. David), mathias.gauduchon@univmed.fr (G. Mathias), maths@mcs.le.ac.uk (M. Andrew), jean-christophe.poggiale@univmed.fr (P. Jean-Christophe).

0022-5193/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2011.05.021

properties (e.g. positive first derivative, vanishing at zero, etc.). An advantage to this method is that we do not need to know the precise shape of functions, which can vary slightly from system to system (e.g. Kuang and Freedman, 1988; Truscott and Brindley, 1994; Korobeinikov, 2009), but this approach has as a serious shortcoming in that only a limited number of models can be treated this way—in particular, a large variety of oscillatory dynamics (e.g. chaotic patterns) cannot be studied without considering a concrete function. For this reason, the conventional approach consists in choosing a particular set of functions and performing the sensitivity analysis by varying model parameters based on these chosen functions. A large amount of literature exists on this topic. The conventional wisdom here is that in the case where the sensitivity of model outcomes to a variation in parameters is small, we can rely on our model. Unfortunately, this "evident" claim can be wrong.

Indeed, recent theoretical studies have shown that different functions with rather close shapes and the same qualitative properties (e.g. positive first derivatives and negative second derivatives, etc.) used in the same model can lead to very different patterns of dynamics (Myerscough et al., 1996). This phenomenon has been referred to as super sensitivity to structure of models by Wood and Thomas (1999). In particular, it was demonstrated that in a case where large variations in parameters produce only small perturbations in model outputs, slight modifications in the mathematical formulations of the functions could lead to catastrophic changes in the system dynamics (Wood and Thomas, 1999; Fussmann and Blasius, 2005). The structural sensitivity can be considered as a generalization of the mathematical concept of structural stability (Kuznetsov, 2004), which states that a dynamical system is structurally stable when a small smooth perturbation does not change its qualitative properties (e.g. the number and stability of equilibria, etc.). Structurally sensitive models can be described as "almost" structurally unstable and we give a more rigorous definition in the next section. Taking into account the possible effects of structural sensitivity on model outcomes become of vital importance, especially with increasing model complexity.

In this paper, we aim to explore in more detail the link between structural sensitivity and structural stability by extending the initial ideas of Wood and Thomas (1999). In particular, we investigate the nature of structural sensitivity in the models, and we argue that it emerges due to the interplay between sensitivity to the variation of parameters and sensitivity to the choice of model functions. We provide a more rigorous definition of structural sensitivity than the original one given by Wood and Thomas (1999), and suggest that a precise measurement of the degree of sensitivity is obtainable based on the Hausdorff distance concept. Finally, we propose a simple semi-analytical test of structural sensitivity where the modeling framework is based on an implementation of ODEs.

Note that occurrence of structural sensitivity can cause another bottleneck in model construction, which is related to the use of experimental datasets in determining an empirically based mathematical formulation of biological processes. The influence of data variability on the parameter estimation of model functions has been largely studied theoretically (Seber and Wild, 2003), as well in the context of ecological applications (e.g. Williams et al., 2002), and on the other hand parameter sensitivity, that is sensitivity of model outputs to variation parameters values, constitutes almost a whole domain of the biological sciences (e.g. Bendoricchio and Jorgensen, 2001). We should say that these two approaches are commonly regarded separately. Yet, for a rigorous investigation into how variations in parameters in experimental data/observations can impact model predictions, one needs to have a precise knowledge of the source of parameter variations, such as the variability due to data sampling. In this paper, we propose an integrative method of directly measuring sensitivity of model outputs to variations in experimental data. We show that sensitivity to data sampling may largely depend on the choice of mathematical formulations retained in models, that is to say, it is closely related to the structural sensitivity phenomenon. Taking structural sensitivity into account allows us to compare "robustness to data variability" among models based on different formulations.

Finally, as an insightful illustration, we will apply our sensitivity analysis methods to a particular biological system – a predator–prey model in a chemostat – where we show the importance of the predator functional response formulation for the patterns of dynamics. To parameterize the functional response, we use data from laboratory experiments on the feeding of protozoa. We will also estimate the robustness of our modeling results with respect to data sampling variability, using our method for directly measuring the sensitivity of the model outputs based on experiments. The paper is organized as follows. In Section 2, we define structural sensitivity and provide a simple test of structural sensitivity, in Section 3, we apply the sensitivity methods to a predator–prey model in a chemostat, and the paper ends with a general discussion and conclusions.

2. Methods for structural sensitivity analysis

2.1. A criterion to detect structural sensitivity

The concept of structural sensitivity is closely related to that of structural stability and the bifurcation theory of dynamical systems. The structural stability definition (Kuznetsov, 2004) states that a given system is structurally stable if infinitely small smooth perturbations of model functions do not result in qualitatively different dynamics, i.e. the initial model and a slightly modified model exhibit identical qualitative asymptotic behaviors and have qualitatively same phase portraits. An example of a structurally unstable system is the famous Lotka–Volterra predator–prey model exhibiting neutral stability. On the other hand, structural sensitivity is characterized by the occurrence of different qualitative and quantitative asymptotic behaviors after small but finite perturbations of the model. In other words, a model is structurally sensitive when in its neighborhood in the functional space of the model it is located close to structurally unstable models. In that case, a perturbation of the system can cross the bifurcation zone, leading to a qualitative modification of the phase portrait. The strength of the perturbation plays an important role in structural sensitivity and a strict definition should include conditions on the limits of the maximal amplitude of such perturbation. However, in this section we would like to provide an illustrative idea of how structural sensitivity emerges in ODEs models and how we can detect its presence based on a simple semi-analytical criterion. In Section 2.3 we give a more strict definition of structural sensitivity.

In order to provide a simple and practical criterion for structural sensitivity, we shall focus here on the equilibrium points of the model. Note that our criterion can be extended to the case of cyclical oscillations as well. We shall consider that an equilibrium point of a given model (M) is hyperbolic, i.e. the eigenvalues of the linearized system at equilibrium have non-vanishing real parts. If the equilibrium is not hyperbolic, then the model (M) is not structurally stable and thus, automatically, it is structurally sensitive to perturbations. Let us assume now that although the equilibrium is hyperbolic, at least one eigenvalue λ_0 has real part close to zero. In practical applications, it is possible that a "small" perturbation could drive the real part of this eigenvalue to cross zero. Such a scenario would lead to a bifurcation and would exhibit structural sensitivity of (M). The amplitude of the perturbation may depend on the distance between $Re(\lambda_0)$ and 0 and on the way the eigenvalues of the Jacobian matrices are affected by perturbations.

Mathematically, the above situation can be rewritten in the following way. We consider an ODEs-based model:

$$\frac{dX}{dt} = F(X) \tag{1}$$

where $X \in \mathbb{R}^n$, and F is a function which is at least $\mathcal{C}^2$ with respect to X. We assume that there is an equilibrium $\overline{X}_0$ and that this equilibrium is hyperbolic. A small perturbation of this model will result in

$$\frac{dX}{dt} = F(X) + \varepsilon G(X) \tag{2}$$

where G is a function which is at least $\mathcal{C}^1$ with respect to X and is bounded in the vicinity of $\overline{X}_0$. It can be shown (implicit function theorem) that system (2) has an equilibrium $\overline{X}_\varepsilon$ close to $\overline{X}_0$ if ε is small enough and

$$\overline{X}_\varepsilon = \overline{X}_0 + \varepsilon\overline{X}_1 + o(\varepsilon)$$

where $\overline{X}_1 = -DF(\overline{X}_0)^{-1}(G(X_0))$ can be calculated from the initial model, its equilibrium and the perturbation map G. We can compute the Jacobian matrix $D(F+\varepsilon G)(\overline{X}_\varepsilon)$ of the perturbed system at $\overline{X}_\varepsilon$ (see Appendix A) and based on the expression obtained we can determine the directions, in the models space, in which the initial model is sensitive. More precisely, we denote by λ_0 the eigenvalue with the smallest real part (taken with absolute value): $|Re(\lambda_0)| \le |Re(\lambda)|$ for all λ eigenvalue of $DF(\overline{X}_0)$. If ε is small enough, there exists an eigenvalue λ_ε of $D(F+\varepsilon G)(\overline{X}_\varepsilon)$ such that

$$\lambda_\varepsilon = \lambda_0 + \varepsilon\lambda_1 + o(\varepsilon) \tag{3}$$

If ε is small enough, then $Re(\lambda_\varepsilon)$ has the same sign as $Re(\lambda_0)$. In practical applications, the amplitude of perturbations depends on the accuracy of the data that we use to validate the model. Such critical perturbation has the meaning of the degree of uncertainty when one parameterizes the model based on the data, thus the value of ε may be estimated based on data variability. The amplitude of the perturbation in the above approach is the norm of εG (the definition of this norm is given in Section 2.2), which in turn depends on ε, thus ε may not be a small parameter and it is possible that the equilibrium $\overline{X}_\varepsilon$ does not exist any more. This means that a bifurcation leading to this disappearance has occurred and thus that the model was indeed structurally sensitive. However, if the equilibrium still exists, we can use the following criterion to analyze its stability. If λ_1 and λ_0 have opposite signs and ε is supercritical, formula (3) shows that λ_ε and λ_0 can have opposite signs, which would result in different qualitative and quantitative dynamics for models (1) and (2). Thus we can conclude that model (1) is structurally sensitive. In the next section, we illustrate how the above theory works for a practical example.

The above criterion can help reveal the existence of structural sensitivity in a given model. Note that such sensitivity can arise from different types of perturbations, mostly due to variation of the parameter values in a given mathematical formulation (which corresponds to the well-known parameter sensitivity), or due to the modification of the mathematical formulation itself. Overall, the structural sensitivity should be considered as a result of the interplay between both mentioned types of perturbation and either of them should not be regarded separately from each other. In the next section, we give a method to quantify the degree of structural sensitivity based on the Hausdorff dimension.

2.2. Measuring the degree of structural sensitivity

Let us consider a model, which we will call the reference model, (M_R). By perturbing (M_R), we obtain a perturbed model (M_P). In order to determine the sensitivity of the reference model we should quantify the impact of the perturbation. Such an impact can be estimated based on comparisons of the models outputs, in particular, by comparing the asymptotic dynamics of the two models. Quantification of impacts of perturbations thus needs two elements: a measure of the distance between (M_R) and (M_P) and a measure of the distance between the outputs of (M_R) and (M_P), respectively. Since asymptotic dynamics of a bounded system can generally be represented by an attractor in the phase space, we suggest considering a distance between the attractors in the phase space, namely the Hausdorff distance.

We denote by d_M the distance between models and d_H the Hausdorff distance between the attractors. First we would like to explain the choice of d_H and state its definition. The point is that the asymptotic dynamics are characterized in the phase space by the ω-limit sets of the model. Such sets are compact and thus a natural distance that can be used to measure the evolution of the system in the phase space is the Hausdorff distance. Let us note that working with the ω-limits instead of considering time series as output reference provides some advantages. For instance, considering an attractor of a system allows us to take easily into account all the state variables at the same time. Moreover, it avoids the influence of initial conditions. Finally, comparing two time series is not always simple since it depends on the time series structure. On the other hand, when comparing attractors in the phase space, we consider two compact sets and the Hausdorff distance becomes a better adapted tool. Let K_1 and K_2 be two compact sets in $\mathbb{R}^n$ with its Euclidian metric d. Their Hausdorff distance $d_H(K_1,K_2)$, defined on the set $\mathcal{K}$ of all the compact sets on $\mathbb{R}^n$, is given by

$$d_H(K_1,K_2) = \max\left\{\max_{y\in K_2}\{d(K_1,y)\}, \max_{x\in K_1}\{d(K_2,x)\}\right\} \tag{4}$$

with $d(A,y) = \min_{x\in A}\{d(x,y)\}$ for any compact set A.

Let us now consider the distance between the models, d_M. There are many ways to define such a distance. For instance, let us assume that in the reference model (M_R) we focus on a particular process which is represented by a reference function g_R, defined on a subset D of the state space. We consider the mathematical expression and the parameter values of g_R to be fixed. We are interested in a perturbation of g_R, leading to a function g_P, also defined on D. The distance between the models can thus be defined by

$$d_M(M_R,M_P) = \int_D |g_R(X) - g_P(X)|\, dX \tag{5}$$

Let us denote by K_R the attractor associated to the reference model for a fixed initial condition and let us denote by K_P the attractor associated to the perturbed model with the same initial condition. The relation between $d_H(K_R,K_P)$ and $d_M(M_R,M_P)$ provides a tool to measure the impact of the perturbation.

Based on the above measuring of distances between the models and the model outcomes we are now able to provide a more rigorous definition of structural sensitivity.

2.3. Definition of structural sensitivity

Let us consider two fixed positive numbers σ and ρ and a reference model (M_R). We denote by $B_\rho(M_R)$ the set of models (M) such that $d_M(M_R,M) < \rho$. For a given initial condition $X \in \mathbb{R}^n$, we denote by $K_R(X)$ its ω-limit with the model (M_R) and by $K(X)$ its ω-limit with the model (M).

We say that (M_R) is ρ-structurally σ-sensitive if there exists $M \in B_\rho(M_R)$ such that one of the following conditions is fulfilled:

(*i*) (M) is not structurally stable;
(*ii*) there exists an initial condition $X_0 \in \mathbf{R}^n$ such that for all X satisfying $K_R(X) = K_R(X_0)$, then $d_H(K_R(X),K(X)) \ge \sigma$.

In other terms, the structural sensitivity occurs when either there is a not structurally stable system in the ρ-vicinity of (M_R) in the space of models, or if an attractor of the system (M_R) is sufficiently deformed (difference $>\sigma$) by a small (size $<\rho$ in the space of models) perturbation (represented by (M)).

For practical purposes, ρ is chosen based on the given accuracy of experimental/field data; σ is the required degree of accuracy of model prediction.

2.4. Data variability and sensitivity analysis

We previously considered a reference model with fixed parameter values and presented some methods to measure its sensitivity to perturbations. As we explained, such perturbations can be due to parameter deviations or to mathematical formulation changes. For a fixed mathematical formulation of the reference model, the parameter values may depend on the datasets used to calibrate it. In this section, we focus on the problems linked to the data variability itself. We propose a method to directly connect the sensitivity of model outputs with the variability of data that have been used to estimate the parameters of the model.

Consider a model *(M)* which includes a particular process. This process is modeled through a known functional relationship $g(X,\theta)$, where X is a vector of state variables and θ is a vector of unknown parameters that control the shape of the curve g. Since these parameters often have ecological interpretations, the aim is to estimate θ as precisely as possible. This is usually achieved using a set of experimental data $\{(X_1,y_1),\ldots,(X_n,y_n)\}$ where the $y_1,\ldots,y_n$ are observations of the process g which is usually sampled at n discrete values $X_1,\ldots,X_n$. The observations of the process g arrive as noisy data such that

$$y_k = g(X_k,\theta)+\varepsilon_k, \quad k=1,\ldots,n$$

where ε_k are considered as random residuals with zero mean and finite variance. The level of noise may strongly depend on the way data are acquired, including frequency sampling, location, measure accuracy, and so on. Starting with these observations, the least-squares estimate $\widehat{\theta}$ of parameter θ is that one that minimizes the following error sum of squares:

$$S(\theta)=\sum_{k=1}^{n}(y_k-g(X_k,\theta))^2$$

In many practical cases, the function $g(X,\theta)$ depends non-linearly on the parameters thus making the regression problem non-linear, so it does not admit analytic solutions and numerical methods are required. Once a realization of $\widehat{\theta}$ is found using the data at hands, one can display the process g and check if the fitting is good. At this step, it can be advisable to quantify the reliability of that fitting. For that matter, the theory of non-linear regression states that, under some appropriate properties of the distribution of random errors, the distribution of the estimate $\widehat{\theta}$ can be found. This distribution allows to construct approximate confidence intervals and to test the quality of the fit to the data. An example of density estimation will be provided further in the application section.

Consider now the outputs of the model *(M)*. This model is connected to the realizations of $\widehat{\theta}$ through the function g. Changing data will change the realization of $\widehat{\theta}$, and will obviously change these outputs. For many practical cases, it becomes of importance to assess how much the model outputs will be modified by data variability. Using an estimated probability distribution of $\widehat{\theta}$ constructed with the dataset, it is possible to draw m values $\{\widehat{\theta}_1,\ldots,\widehat{\theta}_m\}$ which are estimations of θ and to compute the m corresponding output $\{X_1(t),\ldots,X_m(t)\}$ of the model (M). This gives rise to a corresponding family of attractors $(A_k)_{k=1,\ldots,m}$. The effect of data variability is then estimated by implementing a method of calculus of the variance V of this attractor family, such that

$$V=\frac{1}{2m^2}\sum_i\sum_j d_H^2(A_i,A_j)$$

with d_H, the Hausdorff distance between attractors A_i and A_j. In the space of the attractors, the concept of the mean value can be rather ambiguous which prevents the use of a standard variance formula. It is now possible to connect the data variability with the dynamics of the model.

3. The case study: a predator–prey model in chemostat

3.1. Structural sensitivity in a chemostat-type predator–prey model

In this section, we provide an illustrative example of implementation of the above theoretical tools to determine structural sensitivity of a predator–prey model in a chemostat. The chemostat modeling framework is largely implemented in theoretical ecology (e.g. in modeling of planktonic ecosystems, microbial ecology, bioengineering, etc.). Moreover, the chemostat is an apparatus broadly used by experimentalists and that produces numerous datasets on which models can be calibrated. It also produces continuous time series that can be compared to ODE models outputs (Fussmann et al., 2000; Becks et al., 2005). Note also that even if the chemostat models are validated in laboratory experiments and not in a field context, some other ecosystem models show similar mathematical structure (Smith and Waltman, 1995; Thébault and Loreau, 2005). In our study, we focus on the predation process, in particular, the consequences of small variation in the predation function. Note that the problem of formulation of predation function has been widely discussed in theoretical ecology (Arditi et al., 1991; Abrams, 1994; Jeschke et al., 2002).

The model is composed of three ODEs that describe, respectively, the evolution in time of the substrate concentration $x(t)$, the prey population density $y(t)$ and the predator population density $z(t)$. We assume that each population feeds only on one type of resource (the prey for the predator and the substrate for the prey). The nutrient uptake rate $f(x)$ and the functional response $g(y)$ (the number of prey eaten per unit time by a single predator) are represented by generic functions. The model equations are given by

$$\begin{cases} \dfrac{dx}{dt} &= D(x_{in}-x)-f(x)y \\ \dfrac{dy}{dt} &= e_1 f(x)y-g(y)z-Dy \\ \dfrac{dz}{dt} &= e_2 g(y)z-Dz \end{cases} \tag{6}$$

with D the dilution rate in the chemostat, x_{in} is the input substrate concentration within the chemostat reservoir, e_1 is the yield coefficient of prey during consumption of substrate and e_2 is the yield coefficient of predator during consumption of prey. We assume that the generic resource consumption functions $f(x)$ and $g(y)$ belong to $\mathcal{C}^1(\mathbb{R}^+)$. Moreover, when there is no resource in the medium there is no consumption, which means that $f(0)=0$ and $g(0)=0$. We also consider that the more abundant the resource is, the more the consumption of this resource is high. This means that the functions f and g are monotonically increasing: $f'(x)>0$ and $g'(y)>0$.

Thereafter, the specific nutrient consumption by prey $f(x)$ will be modeled with Michaelis–Menten kinetics: $f(x)=v_{max}x/(k+x)$,

with v_{max} is the maximum assimilation rate and k is the half-saturation constant.

A large number of works have been devoted to the analysis of predator–prey models in a chemostat (among many others we can cite Pavlou, 1985; Butler and Wolkowicz, 1986; Smith and Waltman, 1995), and the general dynamics of this type of system is well-known. By applying Theorem 1.5 from Thieme (1994), the chemostat system (6) can be reduced to a two-dimensional model, and it is noteworthy that two-dimensional models are generally structurally stable. Moreover, it can be easily shown that the stability of the positive equilibrium can be given by the sign of the derivative of the prey isocline at equilibrium. This geometrical criterion, that has already been used for generalized Rosenzweig–McArthur model (Freedman, 1976; Brauer and Castillo-Chavez, 2000), can be extended to predator–prey models in a chemostat. Later on, this criterion will allow us to illustrate the mechanism under which a very similar functional response shape can lead to differing qualitative and quantitative behavior of the model.

Here, we are interested on the impact in a functional response expression modification on the chemostat model dynamics. For that, three alternative functional response formulations are considered. They are summarized in Table 1. All these functions have a similar shape. They are concave, monotically increasing and saturate as the prey density becomes high enough. For all of them $a_X = g'_X(0)$ and $a_X/b_X = \lim_{y\to+\infty} g_X(y)$, with $X \in \{h; i; t\}$.

Note that the use of these three functional responses (Holling type II, Ivlev and trigonometric) in a predator–prey model, and the subsequent analysis by Figs. 1–3 very closely follows (Fussmann and Blasius, 2005).

Table 1
The different functional responses.

Functional response	Formulation
Holling (Holling 1959b)	$g_h(y) = \frac{a_h y}{1+b_h y}$
Ivlev (Ivlev, 1961)	$g_i(y) = \frac{a_i}{b_i}(1-\exp(-b_i y))$
Trigonometric	$g_t(y) = \frac{a_t}{b_t}\tanh(b_t y)$

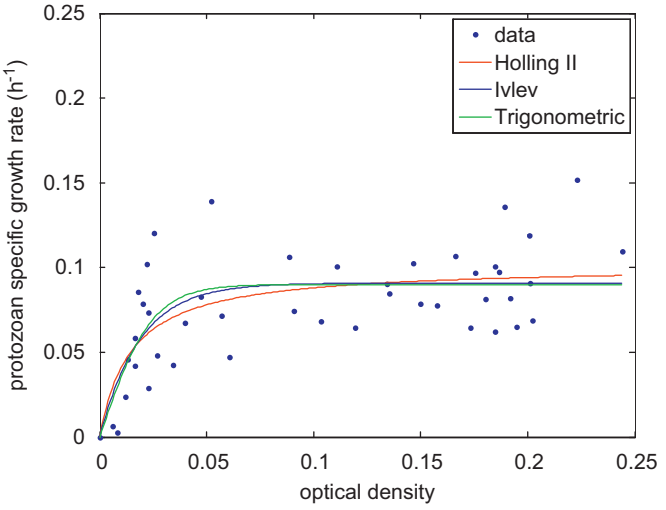

Fig. 1. Data of functional response of protozoa (Canale et al., 1973), and curves of the three functional responses estimated by the simplex method of Nelder–Mead. The functions have very similar shape, even though their mathematical formulations are different.

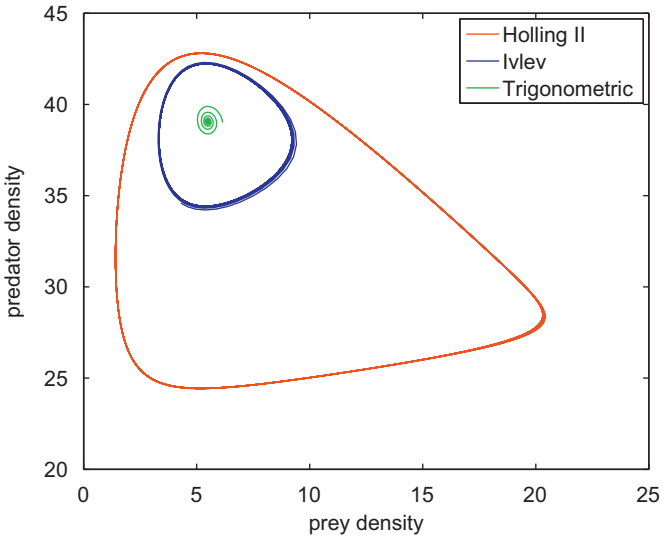

Fig. 2. Phase portrait of the system (6), for the three functional responses, with $D=0.05$ and $x_{in}=130$. The system dynamics are qualitatively and quantitatively different depending on the functional response, with a limit cycle attractor for the Holling type II and the Ivlev function, but an equilibrium for the trigonometric functional response.

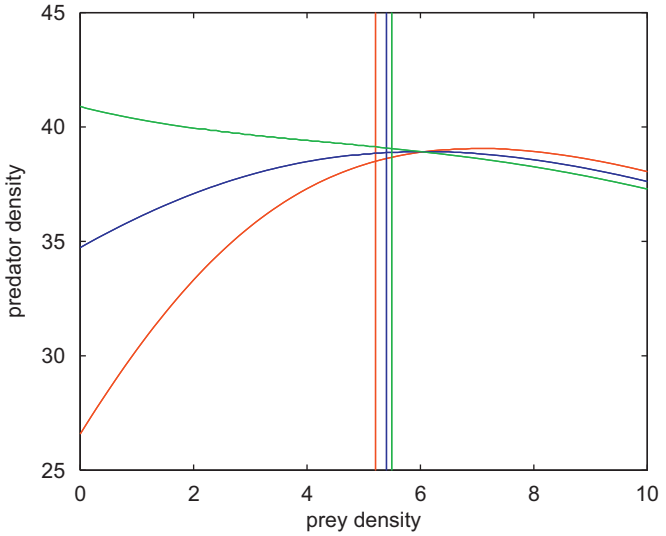

Fig. 3. Representation of prey (curves) and predator (vertical lines) isoclines, for the three functional responses: Holling type II (in red), Ivlev (in blue) and trigonometric (in green), with $D=0.05$, $x_{in}=130$. Predator isoclines are close for the three functions. Prey isoclines deviate from each other giving non-similar slope signs at the equilibrium point, which leads to different system dynamics. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 1 provides an illustration of the three functional responses fitted to a dataset (Canale et al., 1973). One can see from the figure that the fitted functional responses are rather close to each other, even with a set of parameters estimated from real data (see Appendix B for parameter values).

To get an idea of the dynamics produced by each function $g(y)$, a set of simulations was run for different input concentrations x_{in}. It has been observed that an increase of x_{in} leads to a destabilization of the positive equilibrium through a Hopf bifurcation, but the bifurcation does not occur for the same value of x_{in} according to different functional responses. Fig. 2 is the phase portrait of the system showing the dynamics for each functional response when the dilution rate is equal to $0.05\,h^{-1}$, and the input substrate

concentration is equal to 130 mgC/l. For the chosen parameter values, the trajectories simulated based on the Holling and the Ivlev functions settle into a stable limit cycle. By contrast, the dynamics obtained with the trigonometric function reaches an equilibrium quickly. As we early mentioned, this is related to the sign of the prey isocline slope when this curve intersects the predator isocline and gives birth to an equilibrium. In particular, the prey isocline has a positive slope in the case of the Holling and Ivlev functions, but a negative slope for the trigonometric function (see Fig. 3). It is important to note that differences between the three dynamics are qualitative but also quantitative. Indeed even for two cyclic attractors, the amplitudes of the cycles are not the same, with larger oscillations for the Holling than for the Ivlev functional response.

The displayed results underline a sensitivity of the system to the functional response formulation that is important enough to produce quantitative and qualitative dissimilarities in the asymptotic dynamics. The model response to the enrichment, linked directly to an increase of x_{in}, is sensitive to the shape of the predator–prey relations. Thus one would expect that the system is structurally sensitive. In the next subsection, we implement the theoretical methods developed in Section 2 to provide quantitative estimates of structural sensitivity and the effects of data variability.

3.2. Structural sensitivity analysis applied to the chemostat model

We first implement structural sensitivity criterion developed in Section 2.1. In our case we know a priori three different parameterizations of the functional response, and structural sensitivity can be highlighted by considering each formulation as a perturbation of another one. However, generally speaking, we ignore alternative parameterizations and structural sensitivity can be assessed by perturbing the initial function in several directions of models space (in the simplest case, we can consider a linear perturbation). Since the initial three-component model can be reduced to a two-component model, the stability of the perturbed equilibrium can be investigated using the determinant and the trace of the Jacobian. Note that in the given system the determinant is positive as far as the interior equilibrium exists. As such, the sign of the trace allows us to make conclusions on the stability of the equilibrium after perturbation (see the details of the calculus in Appendix B). Our computation allows us to estimate a magnitude of small perturbation of the functional response resulting in structural sensitivity. For example, for $x_{in}=90$, a small linear perturbation of the Holling functional response leads to a destabilization of the positive equilibrium, which can be observed by a change in the sign of the Jacobian eigenvalues, thus the system is structurally unstable.

To get a further insight into the model's structural sensitivity we consider a family of close functional responses. The main objective now is to compare the system sensitivity to a perturbation of the functional response formulation with the sensitivity to a perturbation of the functional response parameters. The impact of both types of perturbation on the system dynamics is quantified based on the method developed in Section 2.2. The distance between the reference model (M_1) and the perturbed model (M_2) is d_M; we consider the space $\mathcal{F}$ of all functions satisfying the model assumptions:

$$\mathcal{F}=\{f\in\mathcal{C}^1(\mathbb{R}^+)/f(0)=0\}$$

We obtain that

$$d_M(M_1,M_2)=\int_0^{y_M}|g_1(y)-g_2(y)|\,dy \tag{7}$$

where g_1 and g_2 are two functions belonging to $\mathcal{F}$ and $y_M=e_1x_{in}$ is the maximum value that may be reached by the prey density y.

For the sake of simplicity, the modification of the functional response formulation is performed on a particular subset of $\mathcal{F}$, namely the linear path between the Holling and the Ivlev functions, where both functions could be used as a reference functional response. We then define the family of functions G_α:

$$G_\alpha=\alpha\hat{g}_h+(1-\alpha)\hat{g}_i,\quad \alpha\in[0,1]$$

where $\hat{g}_h$ (resp. $\hat{g}_i$) is the Holling (resp. Ivlev) functional response g_h (resp. g_i) in which the parameters values are fixed and given in Appendix B. When the α value is continuously moved from 0 to 1 in G_α, the proportion of Holling is modified, respectively, from 0% to 100% in the resulting functional response.

The Hausdorff distance is computed for the formulation perturbation measured with α as well as for the parameter one. When the Holling functional response is used as the reference, α is moved from 1 (Holling) to 0 (Ivlev). Reciprocally, when the Ivlev functional response is the reference, α is moved from 0 (Ivlev) to 1 (Holling).

Since the distance $d_M(G_0,G_\alpha)$ is monotone with α, the maximal perturbation of the functional response is given by the distance $d_M(G_0,G_1)$ that represents the distance measured between pure Holling and Ivlev functional responses (the reference functions). The values of operating parameters D and x_{in} are chosen such that the Holling functional response G_1 produces a cyclical dynamics and the Ivlev functional response G_0 drives dynamics at equilibrium. Thus while α is moving from 0 to 1 the asymptotic dynamics are changing from equilibrium to limit cycle behavior. More precisely, for $\alpha=0.44$, the proportion of Holling function in G_α is large enough to destabilize the system through a Hopf bifurcation. This is illustrated by Fig. 4 that represents the evolution of the ω-limit of the system related to variations of α. On the other hand, the variation of the parameter a_X (resp. b_X) has been performed in both directions by decreasing and increasing a_X (resp. b_X), taking the parameter value given in Appendix B as the starting point. For the sake of brevity we only present here the variation computed along the higher sensitivity direction.

The degree of sensitivity is shown by plotting the distance d_H against the distance d_M (Fig. 5a and b). One can see that in both cases the sensitivity with respect to α is more important than sensitivities to a_X and b_X. Furthermore, the impact of the functional

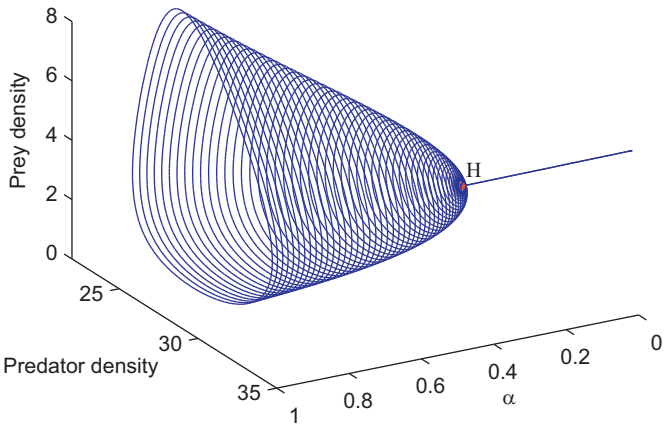

Fig. 4. Bifurcation diagram with $D=0.05$ and $x_{in}=115$. Evolution of the ω-limit of the system is linked to variations of the α value. Change in the functional response formulation from an Ivlev formulation ($\alpha=0$) to a Holling ($\alpha=1$) leads to a destabilization of the model through a Hopf bifurcation (H) for $\alpha=0.442$. The dynamics of the system are numerically studied by using the Matlab bifurcation and continuation toolbox MATCONT (Dhooge et al., 2003).

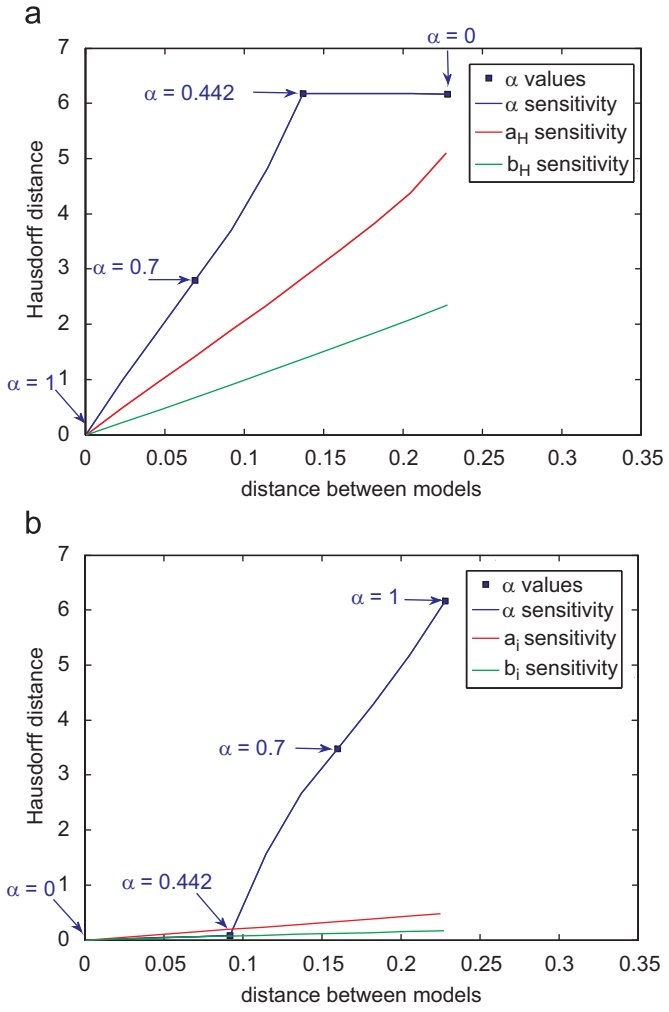

Fig. 5. Hausdorff distances (d_H) simulated for different model perturbation sizes (d_M) produced by variations of α (in blue), a_h (in red) and b_h (in green) values, with the Holling type of response as the reference function (a) and with the Ivlev response as the reference function (b). The system is always more sensitive to changes in the functional response formulation (variation of α) than in the functional response parameter values a_h and b_h. After that α reaches the Hopf bifurcation value 0.442, the system sensitivity to formulation explodes and becomes much higher than the sensitivity to the parameters a_i and b_i. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

response parameter on the system behavior is increasing almost linearly with respect to the d_M, while the sensitivity to the functional response formulation exhibits two phases, each of them being quasi-linear, separated by a sharp increase. The break of the slope occurs when α reaches the Hopf bifurcation value 0.442, at which point a change in the asymptotic behavior of the perturbed system takes place and the α-sensitivity curve is split into two different parts. For $\alpha < 0.442$, the asymptotic behavior of the perturbed system is an equilibrium. In this case, a perturbation of the system drives a slight modification of the equilibrium value which does not have a strong impact on the Hausdorff distance, whatever the reference function is. On the other hand, for $\alpha > 0.442$ the ω-limit set of the perturbed system is a limit cycle for which the amplitude increases drastically, producing large variations in the Hausdorff distance.

Finally, it is interesting to estimate the influence of variability in the data used to reveal the functional response from experiments (Fig. 1) upon the patterns of dynamics predicted by the chemostat system. The estimation of the joint probability distribution of the parameters a_X and b_X, for a given functional response (e.g. Holling or Ivlev functional responses), is obtained by the bootstrap technique. For each functional response, a set of m estimated parameters $\{(a_k,b_k),k=1,\ldots,m\}$ is computed by perturbation of the initial dataset. The bivariate distribution of (a_X,b_X) is estimated by kernel density estimation (Simonoff, 1996). It is then interesting to connect this density function to the bifurcation diagram of the model, in order to observe straightforwardly the changes in the asymptotic dynamics of the model, induced by parameter changes. Fig. 6a displays both the density distribution of parameters a_h and b_h for the Holling functional response, and two bifurcation lines for different values of x_{in}. Let us consider, for instance, the blue curve for $x_{in} = 90$ mg/l. For the parameters located on the left side of this curve the system is at equilibrium, whereas the right side part corresponds to oscillations. Note that the curve splits the bivariate density of (a_h,b_h) in two parts with roughly the same size. This signifies that for some small perturbations of the dataset used to estimate the values of (a_h,b_h), the probability of falling into a particular side is identical. Thus, by using the same experimental dataset, with one formulation, it is possible to get some qualitatively different dynamics. The same observations can be made for the Ivlev formulation with $x_{in} = 130$ mg/l (Fig. 6b).

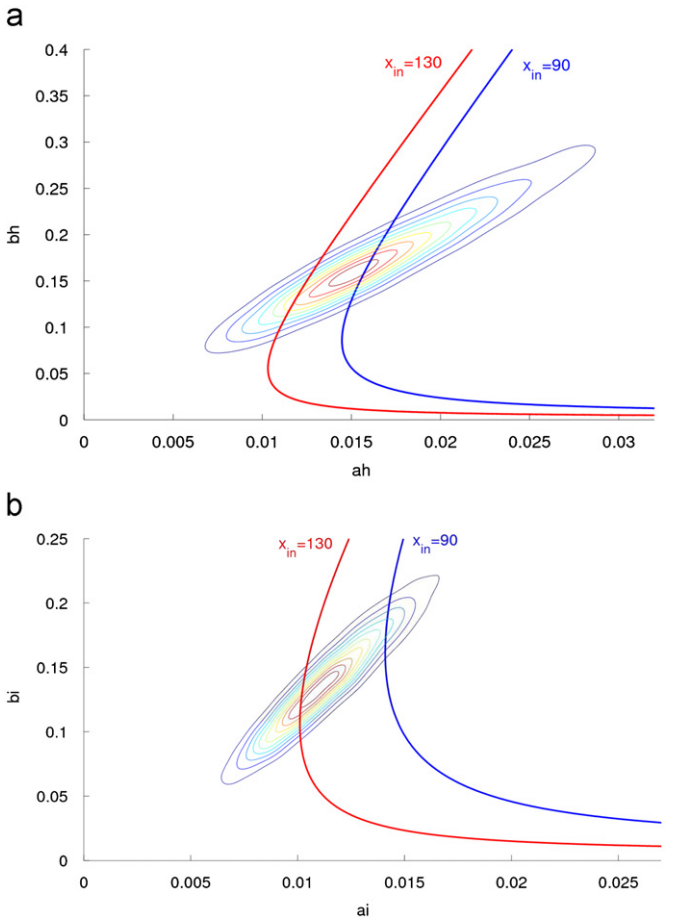

Fig. 6. Bivariate density function of functional response parameters (a_X,b_X), with $X=i$ or h (circular isoclines), and bifurcation diagrams of the model linked to variations of the Holling functional response parameters (a) and of the Ivlev functional response parameters (b). This is performed for $D=0.05$ and $x_{in}=90$ (blue curve), or $x_{in}=130$ (red curve). Whatever the functional response, the variability of the dataset can influence the estimation of the functional response parameters and lead to qualitatively different model dynamics. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

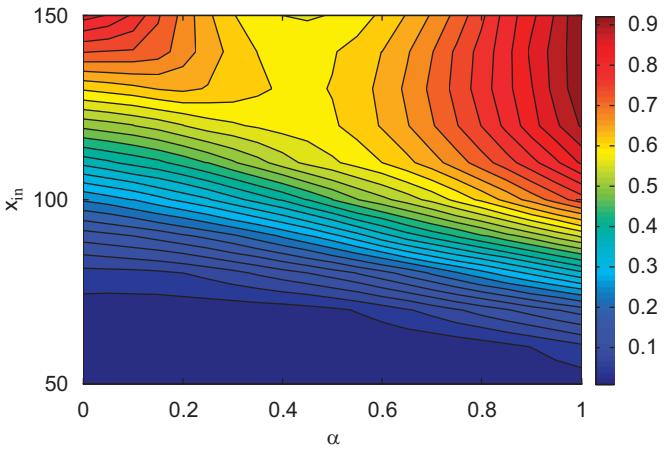

Fig. 7. System variance V computed with 100 pairs of parameters (a_X,b_X) estimated by bootstrap, and for the functional response varying from Holling to Ivlev with variations of the α value from 1 to 0. This is done for x_{in} values between 50 and 150 mg/l. The model output robustness to data variability is stronger when the value of x_{in} is low. For high x_{in}, the use of an "intermediate" functional response ($\alpha = 0.5$), instead of a Holling type II or an Ivlev function, increases the model robustness.

The measure of the effect of data variability on the model output robustness is tackled through the calculus of the variance V introduced in Section 2.4. Fig. 7 displays the computation of V over a set of α values ranging from 0 to 1 (x-axis) and over a set of x_{in} values ranging from 50 to 150 (y-axis). This variance increases with the value of x_{in}, whatever α values. The sensitivity of the system to data variability becomes stronger in the case where the enrichment of the medium is high. For high x_{in}, a weaker variability of the model output is computed for "intermediate" functional responses ($\alpha \approx 0.5$). Thus, the system is more robust to data variability when the functional response used is a linear combination of the Holling and the Ivlev function.

4. Discussion and conclusion

Most current biological models are structurally stable, i.e. infinitely small perturbations will not largely change their dynamics. We argue that to provide robust predictions, one needs the requirement that a given model should not be structurally sensitive. Structural sensitivity encompasses several types of sensitivity that have been already studied separately, such as parameter sensitivity or sensitivity to model formulation (Wood and Thomas, 1999; Fussmann and Blasius, 2005). To summarize, we have revisited the phenomenon of structural sensitivity and provided a more rigorous definition. Based on the refined definition, we developed a practical criterion for the detection of such structural sensitivity in a given model. By extending the method initially elaborated by Wood and Thomas (1999) we proposed a framework to test which type of disturbance (function formulation or parameters) has the greatest impact on the model output, by providing a more general measure of model sensitivity. Finally, we suggested a method that allows us to quantify the impact of data variability on robustness of the model outputs. This approach seems to be quite innovative since it integrates several different steps of the modeling process that could be affected by data variability, and it also enables us to choose which selection of functions is the most robust.

The implementation and illustration of the theory has been performed on a chemostat predator–prey model. Structural sensitivity of this model has been investigated through perturbations of the functional response of the predator, and we found that a relatively small perturbation in the functional response formulation could lead to very different system outputs. We also saw that the chemostat model can be more sensitive to the formulation of the functional response than it is to parameter variations. This can be of a great practical importance since the choice of "correct" functional response for a predator is a matter for debate in the literature regarding how to parameterize predation on different organization levels, and different spatial and temporal scales. Estimation of the functional response of predators is generally empirical, for instance it can be obtained based on fitting of experimental datasets (cf. Fig. 1). The problem of structural sensitivity should be taken into account when estimating the impact of data variability on model predictions. In particular, we have shown based on experimental data for the feeding of protozoa that the dynamics of the chemostat model can be strongly influenced by the data sampling. This impact being even more important in the case of a highly enriched medium.

As we pointed out in the definition, there can be two scenarios of structural sensitivity. When describing a simple criterion in Section 2.1 we considered the case in which a supercritical perturbation results in alteration of the phase portrait of the system (stability loss). The same concerns the case study, where the parameters taken based on data fitting are close to a bifurcation value. This scenario has been reported by Fussmann and Blasius (2005). However, another scenario of structural sensitivity may take place without bifurcation, and it arises because the slight perturbations become largely amplified. This is probably the mechanism underlying the quantitative differences observed in the example proposed in Wood and Thomas (1999). Thus, our criterion of detecting sensitivity given in Section 2.1 does not consider the second case. However, the method to measure the structure sensitivity proposed in our paper will "work" for both scenarios, i.e. it does not require the occurrence of a bifurcation.

In this paper, we have measured model outputs directly in the phase space, by considering system attractors. This approach has several advantages, since the method takes all the variables into account regardless of the time course. Since in modeling in biology we often deal with dissipative systems, the attractors are well defined, and so the Hausdorff distance allows us to measure the quantitative differences between qualitatively different objects. As a result, such comparison does not depend on the initial conditions. Note that it is not always simple to directly compare two time series having different characteristics. For example, when one compares two periodic oscillations with, we need to take into account the difference in amplitudes, the periods and the initial conditions. The attractors in the phase space are always compact sets it makes our approach more efficient in such situations. Nevertheless, the considered approach has some limitations as well. In particular, it can only account for asymptotic behavior and thus neglects any transient behavior. We also loose the reference to the time course (i.e. the time scale of the processes), which in some cases may be crucial.

Note that the suggested simple criterion for detecting structural sensitivity of perturbation in equilibriums can be extended to other types of attractors. For instance, in the case of a limit cycle, we should focus on the eigenvalues of the Poincare map linearization by considering the Floquet multipliers. Furthermore, if a model has several attractor in the phase space, it may be interesting to take this attractors diversity into account in the model output measure. In the case developed in this paper, we fixed the initial conditions, meaning that the attractor considered here is the only possible one within the basin of attraction containing the initial conditions. In the situation where there is an uncertainty regarding knowledge of the initial condition, it could be useful to compare models with different numbers of attractors.

We previously addressed the problem of formulation sensitivity, which raises the problem of formulation choice in models. According to the actual aim of the model, different approaches are used. To enhance the predictive power of models, it is not necessary to gain a full understanding of the system behavior and the structure of parameter space. In order to do this, one needs a robust algorithm able to provide a forecast based on the known set of field data/experiments. An empirical approach can thus be used to choose the parametrization of model functions. The resulting predictive model needs to be robust to slight perturbations and thus we search for models with the lowest sensitivity. The critical perturbation magnitude is determined by the degree of uncertainty about the given process, in particular, it can be determined by the degree of scattering of the available field data. The tools proposed to analyze the structural sensitivity in our paper can be used to check such sensitivity in the existing models. An alternative to the empirical approach for obtaining model functions is the mechanistic one, which is implemented when our objective is to understand biological patterns and process. A mechanistic model can also be sensitive to slight perturbations. In particular, incorporating some mechanisms in a model often leads to more complex systems with additional nonlinearities. Testing a mechanistic model for structural sensitivity will help to reveal the role of different assumptions made when constructing a model based on the outputs, which is important in a cognitive perspective (Poggiale et al., 2010).

Finally, an important question concerns what needs to be done if a model exhibits structural sensitivity for a given set of parameters (and functions). It is evident that the predictions obtained in such a situation cannot be reliable. One could suggest choosing another set of parameters which fits the data less, but is characterized by a smaller degree of structural sensitivity. Another possibility is to suggest including other processes into the model which will result in a decrease of degree of sensitivity (e.g. by considering structured instead of uniform populations, etc.). Alternatively, one can decrease an unjustified model complexity in the case of a large uncertainty about certain processes. We believe, however, that a crucial issue is the understanding of how a natural system will behave in the case where the model describing this system is structurally sensitive. In other words, it would be interesting to see if the structural sensitivity is only an artifact of mathematical modeling (and arises only due to our lack of information on the underlying processes) or if it is an important intrinsic property of biological systems, which could partly explain the unpredictable behavior of many natural systems which is constantly amplified by environmental noise. Addressing this question should definitely be a topic for future investigation.

Appendix A. Jacobian matrix of the perturbed system at the equilibrium

The jacobian matrix of the perturbed system at the equilibrium $\overline{X}_\varepsilon$ is given by

$$D(F+\varepsilon G)(\overline{X}_\varepsilon) = DF(\overline{X}_0)+\varepsilon D^2F(\overline{X}_0)\overline{X}_1+\varepsilon DG(\overline{X}_0)+o(\varepsilon)$$

Since $\overline{X}_1 = -DF(\overline{X}_0)^{-1}(G(X_0))$, we have

$$D(F+\varepsilon G)(\overline{X}_\varepsilon) = DF(\overline{X}_0)+\varepsilon[-D^2F(\overline{X}_0).DF(\overline{X}_0)^{-1}(G(X_0))+DG(\overline{X}_0)]+o(\varepsilon)$$

Appendix B. Calculus of Section 3

B.1. Model parameter values

The different parameter values of the system (6) come from estimations made with a real dataset provided in Canale et al. (1973). The estimations of the values of a_X and b_X ($X \in \{h;i;t\}$) are obtained by fitting each function mentioned above to the dataset.

Table B1
Parameter values and units. mgC means milligram of carbon, mgB means milligram of bacteria and biov means biovolume of bacterivore.

Parameter	Value and unit
D= dilution rate	0.05 h^{-1}
x_{in}= input substrate concentration	50–200 mgC/l
e_1= yield coefficient	0.3 mgB mgC^{-1}
e_2= yield coefficient	1.2 biov l mgB^{-1} ml^{-1}
v_{max}= maximal growth rate	1.6 mgC mgB^{-1} h^{-1}
k= half-saturation constant	16 mgC/l
a_h	1.5×10^{-2} l $biov^{-1}$ h^{-1}
b_h	1.9×10^{-1} l mgB^{-1}
a_i	1.1×10^{-2} l $biov^{-1}$ h^{-1}
b_i	1.5×10^{-1} l mgB^{-1}
a_t	8.2×10^{-3} l $biov^{-1}$ h^{-1}
b_t	1.1×10^{-1} l mgB^{-1}

Parameter estimation is performed by minimizing the sum of the squared distances between each observed data point and the corresponding model value. The minimization has been done by using the simplex Nelder–Mead method (Nelder and Mead, 1965; Lagarias et al., 1998). Thereafter, all the parameters used in the study have been rescaled in order to express the substrate concentration in mg/l, the prey density in mg/l (assuming that one optical density unit is equivalent to 360 mg/l of bacteria (Canale et al., 1973)), and the predator density in biovolume/ml. Their values and units are summarized in Table B1.

B.2. Details of structural sensitivity detection in the chemostat model

The predator–prey system at the positive equilibrium reads

$$F(\overline{X_0}) = \begin{pmatrix} \dfrac{e_1 v_{max}\left(x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}\right)}{k+x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}}\overline{y}-\dfrac{a\overline{y}}{1+b\overline{y}}\overline{z}-D\overline{y} \\ e_2\dfrac{a\overline{y}}{1+b\overline{y}}\overline{z}-D\overline{z} \end{pmatrix}$$

with the following the Jacobian matrix:

$$\begin{cases} DF_{11}(\overline{X}_0) = -\dfrac{v_{max}k}{\left(k+x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}\right)^2}\overline{y} + \dfrac{e_1 v_{max}\left(x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}\right)}{k+x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}}-\dfrac{a}{(1+b\overline{y})^2}\overline{z}-D \\ DF_{12}(\overline{X}_0) = -\dfrac{v_{max}k}{e_2\left(k+x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}\right)^2}\overline{y}-\dfrac{a\overline{y}}{1+b\overline{y}} \\ DF_{21}(\overline{X_0}) = e_2\dfrac{a}{(1+b\overline{y})^2}\overline{z} \\ DF_{22}(\overline{X_0}) = e_2\dfrac{a}{1+b\overline{y}}\overline{y}-D \end{cases}$$

To detect structural sensitivity in the chemostat model, the functional response of the above system is perturbed, and the stability of the perturbed system equilibrium is assessed. The perturbed model at the equilibrium point $\overline{X}_0$ reads

$$(F+\varepsilon G)(\overline{X}_0) = \begin{pmatrix} \dfrac{e_1 v_{max}\left(x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}\right)}{k+x_{in}-\dfrac{\overline{y}}{e_1}-\dfrac{\overline{z}}{e_1e_2}}\overline{y}-\left(\dfrac{a\overline{y}}{1+b\overline{y}}+\varepsilon g(\overline{y})\right)\overline{z}-D\overline{y} \\ e_2\left(\dfrac{a\overline{y}}{1+b\overline{y}}+\varepsilon g(\overline{y})\right)\overline{z}-D\overline{z} \end{pmatrix}$$

Since we are working with two-dimensional systems, the stability of the equilibrium can be found with the determinant and the trace of the Jacobian at the equilibrium point. In the given system the determinant is positive as far as the interior equilibrium exists. Thus, the sign of the trace gives us straightforwardly the sign of both eigenvalues. The trace of the perturbed system is given by

$$T_\varepsilon = \mathrm{Tr}(D(F+\varepsilon G)(\overline{X_\varepsilon}))$$

An asymptotic expansion of T_ε with respect to ε gives

$$T_\varepsilon = T_0 + \varepsilon T_1 + o(\varepsilon)$$

with $T_0 = \mathrm{Tr}(DF(\overline{X}_0))$, and

$$T_1 = \overline{y}\left[\frac{-e_2\overline{z}D^2F_{11y}DF_{12} + \overline{z}D^2F_{11z}DF_{21} + e_2\overline{z}DF_{11} - e_2\overline{z}D^2F_{22y}DF_{12} + e_2DF_{21}DF_{12}}{DF_{12}DF_{21}}\right] - \overline{z}$$

where

$$\begin{cases} D^2F_{11y}(\overline{X}_0) &= \dfrac{\partial DF_{11}}{\partial \overline{y}} = -\dfrac{2v_{max}k}{e_1\left(k + x_{in} - \dfrac{\overline{y}}{e_1} - \dfrac{\overline{z}}{e_1e_2}\right)^3}\overline{y} \\ & \quad -\dfrac{v_{max}k}{\left(k + x_{in} - \dfrac{\overline{y}}{e_1} - \dfrac{\overline{z}}{e_1e_2}\right)^2} + \dfrac{2ab}{(1+b\overline{y})^3}\overline{z} \\ D^2F_{11z}(\overline{X}_0) &= \dfrac{\partial DF_{11}}{\partial \overline{z}} = -\dfrac{2v_{max}k}{e_1e_2\left(k + x_{in} - \dfrac{\overline{y}}{e_1} - \dfrac{\overline{z}}{e_1e_2}\right)^3}\overline{y} \\ & \quad -\dfrac{v_{max}k}{e_2\left(k + x_{in} - \dfrac{\overline{y}}{e_1} - \dfrac{\overline{z}}{e_1e_2}\right)^2} - \dfrac{a}{(1+b\overline{y})^2} \\ D^2F_{22y}(\overline{X}_0) &= \dfrac{\partial DF_{22}}{\partial \overline{y}} = e_2\dfrac{a}{(1+b\overline{y})^2}\overline{z} \end{cases}$$

In our example we take $g(\overline{y}) = k\overline{y}$, with k some constant. For $x_{in} = 90$, the positive equilibrium of the predator–prey model is stable which means that T_0 is negative. The condition for the system to exhibit structural sensitivity is to have T_ε of different sign than T_0. For a linear perturbation a the Holling functional response εT_1 is positive and greater than T_0, leading to an unstable equilibrium. This change in the stability of the equilibrium after some perturbation proves that the system in a chemostat is structurally sensitive.

References

Abrams, P.A., 1994. The fallacies of ratio-dependent predation. Ecology 75, 1842–1850.

Arditi, R., Ginzburg, L.R., Akcakaya, H.R., 1991. Variations in plankton densities among lakes: a case for ratio-dependent models. American Naturalist 138, 1287–1296.

Arhonditsis, G.B., Brett, M.T., 2004. Evaluation of the current state of mechanistic aquatic biogeochemical modeling. Marine Ecology Progress Series 271, 13–26.

Becks, L., Hilker, F.M., Malchow, H., Jurgens, K.H.A., 2005. Experimental demonstration of chaos in a microbial food web. Nature 435 (June), 1226–1229.

Begon, M., Harper, J.L., Townsend, C.R., 2002. Ecology. Blackwell Science, Oxford.

Bendoricchio, G., Jorgensen, S., 2001. Fundamentals of Ecological Modelling. Elsevier Science Ltd.

Brauer, F., Castillo-Chavez, C., 2000. Mathematical Models in Population Biology and Epidemiology. Springer, New-York.

Butler, G.J., Wolkowicz, G.S.K., 1986. Predator-mediated competition in the chemostat. Journal of Mathematical Biology 24, 167–191.

Canale, R.P., Lustig, T.D., Kehrberger, P.M., Salo, J.E., 1973. Experimental and mathematical modeling studies of protozoan predation on bacteria. Biotechnology and Bioengineering 15, 107–728.

Carlotti, F., Poggiale, J., 2010. Towards methodological approaches to implement the zooplankton component in "end to end" food-webs models. Progress in Oceanography 84, 20–38.

Demongeot, J., Francoise, J.P., Nerini, D., 2009. From biological and clinical experiments to mathematical models. Philosophical Transactions of the Royal Society A 367, 4657–4663.

Englund, G., Leonardsson, K., 2008. Scaling up the functional response for spatially heterogeneous systems. Ecology Letters 11, 440–449.

Freedman, H., 1976. Graphical stability, enrichment and pest control by a natural enemy. Mathematical Biosciences 31, 207–225.

Fulton, E.A., Parslow, J.S., Smith, A.D.M., Johnson, C.R., 2004. Biogeochemical marine ecosystem models ii: the effect of physiological detail on model performance. Ecological Modelling 173, 371–406.

Fussmann, G., Ellner, S., Shertzer, K., Hairston Jr., N.G., 2000. Crossing the Hopf bifurcation in a live predator–prey system. Science 290, 1358–1360.

Fussmann, G.F., Blasius, B., 2005. Community response to enrichment is highly sensitive to model structure. Biology Letters 1, 9–12.

Jeschke, J., Kopp, M., Tollrian, R., 2002. Predator functional responses: discriminating between handling and digesting prey. Ecological Monographs 72, 95–112.

Korobeinikov, A., 2009. Stability of ecosystem: global properties of a general predator–prey model. Mathematical Medicine and Biology 26, 309–321.

Kuang, Y., Freedman, H.I., 1988. Uniqueness of limit cycles in Gause-type models of predator–prey systems. Mathematical Biosciences 88, 67–84.

Kuznetsov, Y.A., 2004. Elements of Applied Bifurcation Theory. Springer, New York.

Lagarias, J., Reeds, J., Wright, M., Wright, P., 1998. Convergence properties of the Nelder–Mead simplex method in low dimensions. SIAM Journal on Optimization 9, 112–147.

Morozov, A., 2010. Emergence of Holling type iii zooplankton functional response: bringing together field evidence and mathematical modelling. Journal of Theoretical Biology 265, 45–54.

Morozov, A., Arashkevich, E., 2010. Towards a correct description of zooplankton feeding on models: taking into account food-mediated unsynchronized vertical migration. Journal of Theoretical Biology 262, 346–360.

Myerscough, M.R., Darwen, M.J., Hogarth, W.L., 1996. Stability, persistence and structural stability in a classical predator-prey model. Ecological Modelling 89, 31–42.

Nelder, J., Mead, R., 1965. A simplex method for function minimization. Computer Journal 7, 308–313.

Pavlou, S., 1985. Dynamics of a chemostat in which one microbial population feeds on another. Biotechnology and Bioengineering 27, 1525–1532.

Poggiale, J.C., 1998. Predator–prey models in heterogeneous environment: emergence of functional response. Mathematical and Computer Modelling 27 (4), 63–71.

Poggiale, J.C., Baklouti, M., Queguiner, B., Kooijman, S., 2010. How far details are important in ecosystem modelling: the case of multi-limiting nutrients in phytoplankton–zooplankton interactions. Philosophical Transactions of the Royal Society B 365, 3495–3507.

Seber, C., Wild, C., 2003. Nonlinear Regression. Wiley, New-York.

Simonoff, J.S., 1996. Smoothing Methods in Statistics. Springer, New-York.

Smith, H.L., Waltman, P., 1995. The Theory of the Chemostat. Cambridge University Press.

Thébault, E., Loreau, M., 2005. Trophic interactions and the relationship between species diversity and ecosystem stability. American Naturalist 166, E95–E114.

Thieme, H.R., 1994. Asymptotically autonomous differential equations in the plane. Rocky Mountain Journal of Mathematics 24, 351–380.

Truscott, J.E., Brindley, J., 1994. Equilibria, stability and excitability in a general class of plankton population models. Philosophical Transactions of the Royal Society A 347, 703–718.

Williams, B.K., Nichols, J.D., Conroy, M.J., 2002. Analysis and Management of Animal Populations. Academic Press.

Wood, S.N., Thomas, M.B., 1999. Super-sensitivity to structure in biological models. Proceedings of the Royal Society London B 266, 565–570.