Quantifying uncertainty in partially specified biological models: How can optimal control theory help us?

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Abstract

Mathematical models in biology are highly simplified representations of a complex underlying reality and there is always a high degree of uncertainty with regards to the model function specification. This uncertainty becomes critical for models in which the use of different functions fitting the same dataset can yield substantially different predictions—a property known as structural sensitivity. Thus even if the model is purely deterministic, the uncertainty in the model functions carries through into uncertainty in model predictions, and new frameworks are required to tackle this fundamental problem. Here, we consider a framework that uses partially specified models in which some functions are not represented by a specific form. The main idea is to project infinite dimensional function space into a low dimensional space taking into account biological constraints. The key question of how to carry out this projection has so far remained a serious mathematical challenge and hindered the use of partially specified models. Here we propose and demonstrate a potentially powerful technique to perform such a projection by using optimal control theory to construct functions with the specified global properties. This approach opens up the prospect of a flexible and easy to use method to fulfil uncertainty analysis of biological models.

1. Introduction

Mathematical models of various ecological systems based on differential equations often have the troublesome property of structural sensitivity - in which the use of functional forms which are quantitatively close and qualitatively similar yields contradictory dynamical behaviour (Wood & Thomas, 1999; Fussmann and Blasius, 2005; Cordoleani et al., 2011; Adamson and Morozov, 2014a). Ecological models are particularly vulnerable to structural sensitivity for two main reasons. Firstly, biological processes have a high level of complexity, and so the precise form of any function chosen to represent them cannot be justified because it is necessarily a simplification of the true relation. Secondly, biological data often has substantial error terms, so significantly different functions can fit the same data set equally well. Generally, although structural sensitivity is fairly well acknowledged, the conventional approach in mathematical biology is to stick with a particular functional form, with parameter variation being the full extent of any attempt to deal with uncertainty (Lim et al., 1989; Janssen et al., 1996; Bendoricchio and Jorgensen, 2001). Simply varying parameters, however, is insufficient to check for and deal with structural sensitivity, because models have been shown to be highly sensitive to the formulation of model functions whilst remaining robust with respect to parameter perturbations (Fussmann and Blasius, 2005; Cordoleani et al., 2011). The use of a particular parameterisation cannot even be fully trusted if it derived mechanistically, since such mechanistic derivations always involve many simplifications, so we should not expect it to remain valid if we take into account heterogeneity of a population, larger time or space scales and fluctuating environmental factors (see the Introduction to (Adamson and Morozov, 2012) for a more detailed explanation).

A better approach is to explicitly include the uncertainty in model functions by considering partially specified models (Wood, 2001; Adamson and Morozov, 2014a). In such models, we leave unknown functions unspecified apart from requiring that they satisfy some qualitative criteria inherited from the biological problem being modelled - we may require a function to be increasing, for instance, or to pass through the origin, etc. Note that this approach is based on similar ideas to the seminal works of Gause and Kolmogorov as early as the 1930s (Gause, 1934, Kolmogorov, 1936). Many properties of models are locally determined, such as the number and linear stability of equilibrium points, and it is quite easy to deal with such properties in partially specified models. Note that investigation of the stability of coexistence stationary states is a central part of ecological modelling (e.g. Rosenzweig and MacArthur, 1963; Oaten and Murdoch, 1975; Allen, 2007). Near a (hyperbolic) equilibrium the behaviour of the system is equivalent to that of its linearization, which is completely determined by the value of the equilibrium density and the local values of the unknown functions and their derivatives at this point (Kuznetsov, 2004). We can then treat these values as independent parameters and construct a generalised bifurcation diagram in this new parameter space. This is the basis of the approach known as 'Generalized modelling' (Gross & Feudel, 2006; Yeakel et al., 2011; Kuehn et al. 2012), which links generalised bifurcation diagrams to real world data by considering a transformation of model functions in which the Jacobian depends not on the derivatives of unspecified functions at the equilibrium, but on the 'elasticities', which can theoretically be measured from data. However, since all generalised parameters still need to be measured at equilibrium states, obtaining these measurements can be impossible in the case of an unstable equilibrium; so while we can still try to check the range of the generalised parameters that we consider to be realistic, this will be a somewhat subjective choice.

A more appealing approach would be to consider the entire possible span of the shape of the unspecified biological function—without a need to take measurements from the whole system in which the process is embedded. Based on this concept, a new framework was recently developed to perform bifurcation analysis while taking into account the entire span of the shape of the function (Adamson & Morozov, 2012; 2014a). The crux of the method is to take the entire infinite dimensional space of functions admitted by the data and respecting the global constraints of biological realism, i.e. constraints on the function over its whole domain, and to project it into the generalised bifurcation space. This gives us a closed region in the bifurcation space that consists only of those generalised parameters that can be taken by functions fitting the data and the constraints of biological realism. Using this principle, one can quantify the uncertainty in the system and even carry out a probabilistic bifurcation analysis of the model, for example defining the probability of having oscillations in the case where the exact shape of the function is not specified (Adamson & Morozov, 2014a,b).

This new method of structural sensitivity analysis can rigorously cover all possible model functions, instead of requiring model functions to be restricted to certain (often arbitrary) equations, which makes it particularly useful when modelling biological systems with a high degree of uncertainty. However, its widespread practical application will hardly be possible without resolving the key mathematical question of whether or not functions exist satisfying certain local and global restrictions—that is, they and their derivatives take certain values at certain points, and stay within given bounds across the whole domain. In previous papers on this framework structural sensitivity analysis, all proofs and derivations (using geometric arguments) were limited to the particular case where the global bounds themselves satisfied the properties required from the model function—for instance, for a functional response of Holling type II shape, the quantitative bounds must themselves be increasing, saturating and concave-down functions. Another drawback is that for each set of qualitative and quantitative function properties, we need to carry out analytical calculations which might well be enough to put off more practically-orientated biological modellers, and this inflexibility obstructs the development of software to perform the analysis automatically. Finally, there remains the challenge of constructing appropriate weightings on the neighbourhood of relevant function values in the generalized parameter space: some of these values should be treated as marginal because they correspond to functions that fit the data less well than others, and there is no straightforward way to construct such a weighting.

In this paper, we make a first attempt to develop a general approach to resolve the fundamental issues raised and to point the way towards the development of automated software to make the structural sensitivity framework more accessible for both modellers and biologists. The new approach consists of *approximately* determining whether a valid function satisfying a set of local and global properties exists by constructing a functional which 'rewards' functions for adhering to our criteria of validity (both quantitative and qualitative) and penalises them for straying from the criteria, finding the function which maximises this functional, and checking whether this 'highest scoring' function satisfies the constraints. To find the function maximising the functional, we use optimal control theory—the area of mathematics concerned with finding control parameters of a differential equation which maximise functionals of the resulting solution—in particular, the Pontryagin maximum principle. To demonstrate the efficiency of this method, we consider a Rosenzweig-MacArthur predator prey model (Rosenzweig & MacArthur, 1963, Rosenzweig, 1971) and use our approach to reveal structural sensitivity in this system when we consider functions within complex bounds. We show that our approach outperforms the usual tactic of detecting sensitivity by simply varying parameters of fixed functional forms. Finally, we show how optimal control theory can be used to estimate a relevant 'weighting' of each set of functions used in modelling.

2. General Framework

2.1 Defining a partially specified biological model

Partially specified models represent an attempt to include uncertainty in models by considering one or more model functions as unspecified functions, which aren't given by a particular equation (Wood, 2001). In this paper, we shall consider partially specified ordinary differential equation (ODE) models with only one function left unspecified, $f: [x_{\min}, x_{\max}] \to \mathbb{R}$ where x is a single real-valued variable (note that the method can be easily generalised to an arbitrary number of unspecified functions):

$$\dot{x} = G\big(g_1(\boldsymbol{v}), g_2(\boldsymbol{v}), \dots, g_s(\boldsymbol{v}), f(x)\big), \ \boldsymbol{v} \in \mathbb{R}^n, \qquad (1)$$

$g_1,\dots,g_s$ are fully specified functions, with only their parameters being unknown; the function G determines how the subfunctions are assembled together, and is assumed to be known. Our aim is to check whether the model is sensitive to the functional form of f, and thereby determine to what extent we can trust the predictions of a corresponding model with a precise equation chosen for f. In order to link the partially specified model to data and theory we consider that f is required to remain between two boundary functions:

$$h_{\text{low}}^{0}(x) \leq f(x) \leq h_{\text{high}}^{0}(x), \qquad (2)$$

and satisfy some qualitative properties, which take the form of bounds on its derivatives:

$$h_{\text{low}}^{j}(x) \leq f^{(j)}(x) \leq h_{\text{high}}^{j}(x). \quad j = 1, \dots, p. \quad (3)$$

Note that the bounds for the derivatives $h_{\text{low}}^{j}(x), h_{\text{high}}^{j}(x)$ can be, in principle, piecewise smooth, i.e. have jumps at a number of points. An exotic example of two boundary functions h_{low}^{0} and h_{high}^{0} are show as the red curves in Figure 2, together with a function bounded by them. The bounds on f can be specified in different ways, depending on the situation: they may be taken from experimental data, in which case they will be the corresponding error bounds representing, say, 95% confidence intervals, or they could be used as a way of representing a purely hypothetical data set in our analysis, so that we can check how the model reacts to changes in the whole data profile. Alternatively, h_{low}^{0} and h_{high}^{0} can be built by taking a fixed absolute or relative distance ε from some original 'base function', which may itself have parameters—varying these parameters will shift the bounds and we can check how the model reacts to a change in parameters, without needing to fix a parameterisation. Bounds on even the first derivatives are difficult to obtain from data, but may follow from biological theory or hypothesis—e.g. a feeding term might need to be an increasing function of the available food, and may saturate due to food handling time requiring a negative second derivative.

We may also want to restrict f and its derivatives at a certain set of values:

$$\begin{gathered} f^{(j)}(x_1) = f_1^{j}, \qquad j \in I_1 \\ \vdots \\ f^{(j)}(x_m) = f_m^{j}, \qquad j \in I_m, \end{gathered} \qquad (4)$$

Where the I_i are indexing sets which determine which derivatives of f we restrict at each point $x_i, i = 1, \dots, m$. We should introduce these exact local restrictions when we have (or want to postulate) exact information on the behaviour of the function at certain points. By far the most common example in biology is that functions should be zero at the origin, since it often makes no sense that there can be growth, feeding, mortality etc. with no population to begin with. In another case, if we know a function should have an inflection point, then we should set $f''(x_i) = 0$, where x_i is the inflection point. Since we usually can't know the exact value at which we have an inflection point, we should treat x_i as a parameter of the investigation in this case, to be varied over a range.

Naturally, it is more complicated to investigate partially specified models than to investigate models in which all functions are fixed, and innovative ways are required to deal with this difficulty. However, when we have high uncertainty in our model functions, the use of only fully specified models may not be sufficient. Consider that most generic function spaces are infinite dimensional. If we have a partially specified model and choose a particular function, determined by two parameters, say, to represent an unspecified function, then this only encompasses a 2-dimensional subset of the infinite dimensional space of valid functions. So unless we have a very good reason for choosing this parameterisation, its analysis is likely to be highly misleading (Fussmann and Blasius, 2005; Cordoleani et al., 2011). If we can work directly with the partially specified model our analysis will be general, as any such model necessarily includes every model with a particular valid parameterisation as a special case.

2.2 Structural sensitivity analysis of partially specified models

The framework first introduced in (Adamson and Morozov, 2012) for the investigation of partially specified models centres on the fact that for many system properties we do not need to know the entire shape of the constituent functions. For instance, local to a hyperbolic equilibrium, system behaviour is determined solely by the values taken by the functions and their derivatives at this equilibrium (Kuznetsov, 2004). In the notation of section 2.1, we only need to know the values x^* and $f(x^*)$ to determine if x^* is an equilibrium density. Given these values and $f'(x^*)$, we can compute the Jacobian matrix at this equilibrium and check whether the real parts of all its eigenvalues are negative, and so determine the linear stability of the equilibrium without needing to refer to the function f itself. In this way, we can construct bifurcation diagrams in a 'generalised parameter space', in which x^*, $f(x^*)$ and the relevant derivatives of f at x^* are treated as if they were model parameters. This idea is the basis of both the generalized modelling framework (Gross & Feudel, 2006; Kuehn et al. 2012) and earlier classical works (Gause, 1934, Kolmogorov, 1936).

Given the generalised parameter values x^*, $f(x^*)$, …, $f^{(p)}(x^*)$, the local bifurcation analysis is relatively simple. Taking into account constraints (2)-(4), however, it's clear that only a finite region of the generalized bifurcation space can match the data. For some of these values, no function will exist that satisfies the imposed global and local constraints: consider Fig. 2, if $x^* = 0.1$ and $f(x^*) = 0.9$, then in this case clearly no function can take these values and lie within the boundaries. A generalised bifurcation plot should therefore look like Figure 3—with the dark blue region representing impossible generalised parameter values, surrounding the finite region of possible ones. Finding this finite region is then the main challenge—afterwards we can determine the range of possible system behaviour, and compute the relative sizes of the domains of this region which correspond to different dynamical regimes. In the case where different domains have comparable size (or measure), we have significant structural sensitivity in the model. Thus, the main idea of this framework for structural sensitivity analysis is finding a *projection:* from the infinite dimensional space of functions which fit the data and theoretical assumptions, onto the low-dimensional generalised bifurcation space.

To find such a projection, we need a way to determine whether, given a set of the values x^*, $f(x^*)$, …, $f^{(p)}(x^*)$ which determine the local dynamics, they are attained by a function satisfying constraints (2)-(4). Equivalently, we include x^* as one of the points in (4), at which we locally restrict f, f',…,$f^{(p)}$, and check whether *any* function exists satisfying these new constraints. Once we have a criterion for determining the existence of such a function, we can scan the generalised bifurcation space consisting of the values x^*, $f(x^*)$, …, $f^{(p)}(x^*)$, including each set of these values in turn in the local restrictions given by equation (4), and checking whether a function satisfying these restrictions exists. If so, these values are taken by a function that is valid for the data set and theoretical constraints, so must lie in the finite region giving the possible system behaviour.

The main mathematical challenge for the framework is to prove the existence of a function f which respects a set of global and local constraints (equations (2)-(3) and (4), respectively). In (Adamson and Morozov, 2013, 2014a) a geometric approach was used to obtain such a projection up to the first derivative for a particular class of qualitative constraints, in the case where the boundaries h^0_{low} and h^0_{high} are built by taking a fixed distance ε from a given base function—where the base function is itself a valid model function and the bounds for first and the second derivatives are constant. However, in general the bounds h^0_{low} and h^0_{high} shouldn't themselves be expected satisfy the global derivative constraints (3) (if they are error bounds taken from data, for instance), in which case this geometric approach is not valid. Also, it is desirable to estimate a weighting on the region of the generalised bifurcation space which measures how well the functions corresponding to these points can fit the data, which is not easy to do in the geometric framework. Finally, the geometric method is case specific in the sense that each set of qualitative and quantitative function properties needs its own analytical criteria for the existence of functions, which is a significant obstacle to the creation of software which would allow non-mathematicians to implement the method.

2.3 Determining the existence or not of a function satisfying global/local constraints

One potential approach to address the issues mentioned above and make the framework of (Adamson and Morozov 2012, 2014a) more flexible is to use methods from optimal control theory to find the projection from the space of valid functions into the generalised bifurcation space *approximately*. Here we shall propose an algorithm for doing this. In this section, we consider the equilibrium x^* along with $f(x^*),\ldots,f^{(p)}(x^*)$ to be fixed (i.e. we deal with one set of generalised parameters at a time), and to be already included in the set of local restrictions given by (4). Therefore the question of whether $x^*, f(x^*), \dots, f^{(p)}(x^*)$ can be attained by a valid function is reduced to the question of whether or not there exists a function f satisfying a set of global and local constraints in the form of equations (2)-(4).

In order to address this problem approximately, we apply optimal control theory. Broadly speaking, optimal control theory aims to find the parameter input of a system of differential equations such that the solution maximises an objective functional, which scores solutions of the system based on some desirable criterion (alternatively we can aim to minimise a cost functional penalising undesirable criteria). The basic idea to check for the existence of a function f satisfying (2)-(4) is to create an objective functional that rewards functions for adhering to the global bounds (2)-(3) and build a set of differential equations that yield a candidate for the function f as a solution (in such a way that all solutions must satisfy the local restriction provided by (4)). The currently considered values $x^*, f(x^*), \dots, f^{(p)}(x^*)$ can then be represented by the function taking them which scores best in its adherence to the global constraints—if this function does not satisfy the global constraints, it can be assumed that no function attaining these values will. In this case, we should exclude this set of values from the region of relevant generalised bifurcation parameters because they cannot be taken by a valid function that fits the data and satisfies the theoretical assumptions. If the optimal function taking the values $f(x^*), \dots, f^{(p)}(x^*)$ does satisfy the global constraints, then we've found such a valid function for these values, so this set of values must lie inside the region of relevant generalised bifurcation parameters. The remainder of this subsection concerns the construction of such an optimal control problem. Readers who are more interested in the applications of the method need not trouble themselves too much with the precise details, and may wish to skip to 2.4.

We specify our objective functional as taking the following form:

$$I\left(f, f', \dots, f^{(p)}, f^{(p+1)}\right) := \int_{x_{\min}}^{x_{\max}} \sum_{j=0}^{p} F_j\left(x, f^{(j)}(x)\right) + \eta \cdot R\left(f^{(p+1)}(x)\right) dx, \qquad (5)$$

where the F_i are given by:

$$F_i = \frac{1}{\left(e^{\gamma\left(h_{\text{low}}^{j}(x) - f^{(j)}(x)\right)} + 1\right) \cdot \left(e^{\gamma\left(f^{(j)}(x) - h_{\text{high}}^{j}(x)\right)} + 1\right)}, \qquad j = 0, \dots, p. \qquad (6)$$

The objective term for each derivative $f^{(j)}(x)$ is chosen as a smooth approximation to a step function with a high value within the bounds $h_{\text{low}}^{(j)}(x)$ and $h_{\text{high}}^{(j)}(x)$ and a low value without. The parameter γ describes the width of the transition layer at the boundary around $h_{\text{low}}^{(j)}(x)$ and $h_{\text{high}}^{(j)}(x)$, with higher values of γ yielding narrower layers and a steeper transition. The inclusion of the $(p+1)$-th derivative will be discussed later, along with the form of R. Such a function F_i is shown in Fig.1: it imparts high values to functions which satisfy the constraints, without discriminating too much between functions that do (as would be the case if F_j had a pronounced peak, for instance). The functional I will yield a higher value for a function f if it satisfies constraints (2)-(3) for more x-values. Note that the construction of this functional involves a softening of the hard bounds in (2)-(3): we no longer demand our function to satisfy these inequalities strictly. Therefore we could dispense with the hard bounds in (2)-(3) altogether, and replace (6) with a normal distribution or a similarly peaked function, without changing the framework. In this case, instead of trying to determine the set of all values in the generalised bifurcation space that could be taken by functions fitting the hard bounds, we would be directly assigning these points a score based on how well their optimal functions fit a probability distribution.

Boundary layers which are too narrow can result in ill-posed problems related to non-uniqueness of the optimal solution. They can also result in computational difficulties, since in the vicinity of the optimal solution close functions f can provide very close values of I—as the gradients of the objective functions are too small (i.e. the top of the function in Fig 1. is too flat). To transform an ill-posed problem into a well-posed problem we use the standard framework based on Tikhonov regularization (see Tikhonov and Arsenin (1977) for a general introduction into Tikhonov's regularization method). In particular, we insert into the objective functional a function R of the highest unrestricted derivative, which is multiplied by a small parameter $\eta \ll 1$, so that it does not affect the value of I too strongly. In our computation we choose the following equation for R

$$R\left(f^{(p+1)}(x)\right) := -\left(f^{(p+1)}(x) - \frac{C}{2}\right)^{2\sigma}, \qquad \sigma \in \mathbb{N}. \tag{7}$$

This formulation will have a pronounced peak at $\frac{C}{2}$ (indeed, this is how Tikhonov regularisation works), so it should give the mid-point in the range of the variation of $f^{(p+1)}$. In the case where we do not have information on this derivative, it is natural to consider C to be zero, as we assume in this paper. However, we should stress that variation of this parameter within a broad range does not strongly affect the results when η is sufficiently small. The parameter σ determines the width of the range of $f^{(p+1)}$ which is allowed. In this paper, we set σ=1 for the sake of simplicity.

In order to represent the problem of finding the function maximising (5) as an optimal control problem, we consider the trivial differential equation linking f and each of its derivatives in turn. We treat the highest derivative considered, $u = f^{(p+1)}(x)$ as the control parameter. The question now is which input $u(x)$, after being integrated $p+1$ times, yields the function which maximises I? Details are provided in Appendix A. Taking the notation the notation $y_j = f^{(j)}$ for the derivatives of f, and applying the Pontryagin maximum principle, we find that the solutions to the optimal control problem must satisfy the following boundary value problem:

$$
\begin{aligned}
\dot{y_0} &= y_1, \\
\dot{y_1} &= y_2, \\
&\vdots \\
\dot{y_{p-1}} &= y_p, \\
\dot{y_p} &= -\frac{\psi_p}{2\eta} - \frac{C}{2}, \\
\dot{\psi_0} &= \frac{\partial F_0}{\partial y_0}, \\
\dot{\psi_1} &= -\psi_0 + \frac{\partial F_1}{\partial y_1}, \\
&\vdots \\
\dot{\psi_p} &= -\psi_{p-1} + \frac{\partial F_p}{\partial y_p}.
\end{aligned}
\tag{8}
$$

To incorporate the local restrictions (4), we partition the whole domain $[x_{\min}, x_{\max}]$ by the points: $x_{\min} < x_1 < \cdots < x_m < x_{\max}$. Given a subdomain $[x_i, x_{i+1}]$, the derivatives in (4) which are fixed at x_i and x_{i+1} must serve as boundary conditions:

$$y_j(x_i) = f^{(j)}(x_i) = f_i^j, \; j \in I_i. \tag{9}$$

The rest of the boundary conditions are given by setting $\psi_j(x_i) = 0$ whenever $j \notin I_i$, and the jth derivative is therefore left unfixed. In this way we obtain $2p$ boundary conditions over each interval, and each of our boundary value problems is therefore well-posed.

2.4 Demonstration model

In order to demonstrate the method, we shall use it to conduct an investigation into structural sensitivity of the Rosenzweig-MacArthur predator-prey model (Rosenzweig & MacArthur, 1963, Rosenzweig, 1971). This is a classical model in mathematical ecology, due both to its elegance and to the complex dynamics it can admit. The equations for the model are:

$$
\begin{aligned}
\dot{x} &= g(x) - f(x)z, \\
\dot{z} &= kf(x)z - dz,
\end{aligned}
\tag{10-11}
$$

where x is the prey density and z is the predator density; g is the growth term (including natural mortality) for the prey species, while f is the functional response of the predator—the rate of prey consumption as a function of prey density. For our particular choice of growth term g, we choose the logistic function, $g(x) \coloneqq rx\left(1 - \frac{x}{K}\right)$. The parameters of the model are interpreted as follows: r is the initial prey growth rate; K is the carrying capacity of the prey; k is the trophic efficiency coefficient and d is the natural predator mortality rate.

We assume that the functional response f is unspecified, but we require it to satisfy the following restrictions:

$$f(x) \geq 0 \;\; \forall x \in [0, x_{\max}], \tag{12}$$

$$f'(x) \geq 0 \;\; \forall x \in [0, x_{\max}], \tag{13}$$

$$A \leq f''(x) \leq \; 0 \;\; \forall x \in [0, x_{\max}], \tag{14}$$

$$f(0) = 0. \tag{15}$$

Condition (12) signifies that negative feeding is not possible; (13-14) comes from the assumption that f is a functional response with similar shape to a Holling type-II function, therefore it should be increasing—more prey should always result in a greater consumption rate—and should be saturating (Gentleman et al., 2003)—the predator gets diminishing returns for large prey numbers due to the handling time; (15) is a natural requirement. To demonstrate that our method works for complex error bounds h^0_{low} and h^0_{high}, we have chosen somewhat exotic functions shown by the red lines in Fig. 2. We should emphasise that these bounds are chosen for demonstration because of their complexity rather than because they are intended to represent bounds resulting from an actual data set. The formal bounds on $f'(x)$ and $f''(x)$ are, respectively, $h^1_{\text{low}} = 0$, $h^1_{\text{high}} = 100$ and $h^2_{\text{low}} = A = -20$, $h^2_{\text{high}} = 0$.

Our aim is to check the sensitivity of the stability of the interior equilibrium in this partially specified system to the choice of functional response term. The model is well studied in the literature (Allen, 2007) with the key results here being that we only have a single interior equilibrium, this equilibrium is linearly stable if

$$r\left(1 - \frac{2x^*}{K}\right) < f'(x^*)z^*.$$

For a given set of model parameters our generalised bifurcation space will consist only of the values $x^*$and $f'(x^*)$, since (11) implies that $f(x^*) = \frac{d}{k}$. We need to project our space of valid functions onto this space by scanning the x^* and $f'(x^*)$ values (we set $f'(x^*)$=f_*^1) and, for each of these points, determining whether there exists a function taking these values while still satisfying the restrictions on the derivatives and staying within the upper and lower error bounds. To do this, we apply the approach outlined in Section 2.3, and aim to find the function which maximises the functional:

$$I(f, f', f'', f''') \coloneqq \int_0^{x_{\max}} F\big(x, f(x)\big) + G\big(x, f'(x)\big) + Q\big(x, f''(x)\big) + \eta R\big(f'''(x)\big) dx, \tag{16}$$

where F, G and Q are given by equation (6) (with $F = F_0$, $G = F_1$, $Q = F_2$), with $\gamma = 50$. R is defined as (7), with $C = 0$. As our local restrictions are at $x = 0$ (from (15)) and $x = x^*$ (we fix x^*, $f(x^*)$ and

$f'(x^*)$ because we are checking if they correspond to a valid function), we split the domain into $[0, x^*]$ and $[x^*, x_{\max}]$, and apply the Pontryagin maximum principle to obtain a boundary value problem over each of these domains, as per Section 2.3. More details of how we apply the framework outlined in Section 2.3 here, along with the equations and conditions for the boundary value problem, are contained in Appendix B.

The resultant non-linear boundary value problem is not easily investigable analytically, but several numerical techniques exist for the solution of such problems. The method we apply here is the nonlinear shooting method, a standard technique which is covered in many textbooks on numerical analysis, for instance (Burden and Faires, 2001). In this way, we can compute the function $\tilde{f}$ which best fits our qualitative and quantitative restrictions given that $\tilde{f}(x^*) = \frac{d}{k}$ and $\tilde{f}'(x^*) = f_*^1$. An example of such an optimal function $\tilde{f}$, together with the constraints used, is shown in Fig.2. To decide whether or not to include the point (x^*, f_*^1) in our projected domain in generalised bifurcation space, we check whether $\tilde{f}$ satisfies constraints (12)-(14). If so, then (x^*, f_*^1) is attained by at least one valid function, $\tilde{f}$, and so should be included in the projected domain. If not, we can reasonably assume no function attaining $\tilde{f}(x^*) = \frac{d}{k}$ and $\tilde{f}'(x^*) = f_*^1$ exists which satisfies (12)-(14)—if such a function did exist, then it should maximise I—so (x^*, f_*^1) should be excluded from the projected domain.

3. Implementation of the method

3.1 Stability plots

For the Rosenzweig-MacArthur model with the function bounds shown in Fig.2, and parameter values $d = 0.1$, $k = 0.3$, and $K = 0.58$, the region of generalised bifurcation space corresponding to valid functions is shown in Fig.3. In this figure, dark blue indicates that the optimal function which takes these x^* and $f'(x^*)$ values fails to satisfy constraints (12)-(14), so we conclude that no valid function taking these values exists. For those values which correspond to valid functions, green indicates that the nontrivial equilibrium will be stable, while red indicates that it will be unstable. The light blue region represents the area that can be covered by considering only functions with the Monod or 'Holling type-II' parameterisation

$$f(x) = \frac{ax}{b + x}, \tag{17}$$

and varying the parameters a and b as far as the function stays within the constraints. Note that the Monod function is very popular in ecological literature (Gentleman et al., 2003).

From Fig.3 it is immediately clear that there is a high degree of structural sensitivity in the system—the presence of both green and red regions in our projected domain indicates that the system can admit both a stable and an unstable interior equilibrium when different valid functional responses are chosen. It is also clear that our method outperforms the approach of varying parameters of the fixed Monod function, since our projected domain covers the entirety of the light blue region, and more besides. The reason for this is that varying the parameters of the Monod function, or of any other fixed function, can only perturb the function in an extremely constrained way, which artificially restricts the range of values x^* and $f'(x^*)$ that can be taken by such a function while staying between the upper and lower bounds. Fixing the function to a particular equation means that local perturbations cannot be made without inducing global perturbations elsewhere. For example, with the Monod function, the derivative at some x^* could be increased by decreasing the half saturation constant, b. But because we have fixed our function to a precise equation, this decrease in b will necessarily increase the slope of the function at the origin, and might take the function above the upper bounds. Similarly, increasing the maximal feeding rate a may take the function above the upper bound at high values of x. In the case of Figure 3, since the light blue region is entirely contained in the stable region, all Monod functions fitting our data range will yield a stable interior equilibrium and varying its parameters will not detect the structural sensitivity in the system.

3.2 Probabilistic bifurcation analysis

Based on the stability plot shown in Fig.3 which demonstrates the existence of structural sensitivity in the system, one can quantify this sensitivity by introducing measures of the probability of having different model behaviour, i.e. a stable and an unstable equilibrium. Introducing a probability density function on our generalised bifurcation space also allows us to follow changes in the probability of having different dynamics with variation of other models parameters. In the simplest case, we can consider a uniform probability distribution of functions, in which case the probability of having a certain type of model behaviour will be given by the area/volume of the corresponding proportion of the domain in generalised bifurcation space taken by valid functions. For instance, in our investigation, the probability of having a stable equilibrium would be computed from Fig.3 by taking the ratio between the area of the green region and the area of the red and green regions combined.

One of the salient features of the Rosenzweig-MacArthur model is a loss of stability of the interior equilibrium through a Hopf bifurcation as the carrying capacity, K, of the prey species is increased—a phenomenon known as the 'paradox of enrichment' (Oaten and Murdoch, 1975; Fussmann and Blasius, 2005). Therefore it is worthwhile to consider how the probability of having a stable equilibrium in our partially specified model varies with K (fixing all the other parameters for simplicity). This is given by the blue curve in Fig.4. We see that for low carrying capacities, the probability of stability is 1, as in this case the entire projected domain in generalised bifurcation space yields stable dynamics. As K is increased, we then see the possibility arises of having an unstable equilibrium, as the Hopf bifurcation curve enters our projected domain as is the case in Fig.3. A further increase in K causes the red region of the projected domain to advance until it fills the entire domain, at which point all valid functional responses will yield an unstable interior equilibrium. Therefore we can still observe the paradox of enrichment in the partially specified Rosenzweig-MacArthur model, but as a monotone decrease in the probability of observing a stable equilibrium, rather than a concrete stability loss, as would be the case in the standard Rosenzweig-MacArthur model, with all model functions fixed. The bifurcation taking place via a shift in probability reflects the fact that we retain the uncertainty in the formulation of the functional response throughout our analysis.

3.3 The degree of structural sensitivity

To quantify the structural sensitivity in the model, one can evaluate the 'degree of structural sensitivity' which is defined as twice the probability of two randomly chosen functions (according to the probability distribution we are considering in the generalised bifurcation space) yielding conflicting model behaviour (Adamson & Morozov, 2012). In the case that we are interested in equilibrium stability, and considering a uniform distribution over the points in the projected domain for simplicity of notation, this will be given by:

$$\Delta := 4 \cdot \frac{V_{\text{stable}}}{V_{\text{total}}} \cdot \left(1 - \frac{V_{\text{stable}}}{V_{\text{total}}}\right), \tag{18}$$

where V_{stable} is the volume (or area) of the stable region of the projected domain, and V_{total} is the volume of the total projected domain. In the next section we shall consider how to improve the degree of structural sensitivity by weighting points according to how well the corresponding model functions can fit the constraints, instead of assuming a uniform distribution. Note that the degree of sensitivity: i) will equal 0 if the stable region takes up either all or none of the projected domain; ii) has a maximum of 1, which is attained whenever the stable region takes up exactly half of the projected domain; iii) essentially only depends on $V_{\text{stable}}/V_{\text{total}}$, the probability of having a stable equilibrium; iv) will be unaltered if we replace the volume of the stable region with the volume of the unstable region in the calculation, since we necessarily have:

$$\frac{V_{\text{unstable}}}{V_{\text{total}}} = 1 - \frac{V_{\text{stable}}}{V_{\text{total}}}, \tag{19}$$

and therefore get the same degree of sensitivity whether we compute the probability of having a stable equilibrium or an unstable one, as should be expected. To demonstrate how the degree of structural sensitivity in the partially specified model varies with the probability of having a stable equilibrium, we have plotted the dependence of the degree of sensitivity on the carrying capacity K as the red curve in

Fig.4. Note that the degree of sensitivity will also depend on the other model parameters which are fixed in this figure.

3.4 Weighting functions in the generalised bifurcation space

Quantification of the degree of sensitivity of a partially specified model may depend strongly on the choice of the probability density function assumed in the generalised bifurcation space. The assumption of a uniform probability distribution in (18) is somewhat hard to justify, so we should introduce a probability distribution ρ that *weights* points $\left(x^*, f'(x^*)\right)$ according to how well functions taking these values can fit the constraints. In this case, the degree of structural sensitivity will become

$$\Delta := 4 \cdot \frac{\int_{V_{\text{stable}}} \rho \, dV}{\int_{V_{\text{total}}} \rho \, dV} \cdot \left(1 - \frac{\int_{V_{\text{stable}}} \rho \, dV}{\int_{V_{\text{total}}} \rho \, dV}\right), \tag{20}$$

One way to introduce a weighting of points in functional space is to use the concept of 'functional density' (Adamson & Morozov, 2012). The functional density can be defined as the average (over the x-values) fraction of the possible values that has some valid function taking the values $\left(x^*, f'(x^*)\right)$ passing through it—i.e. the average proportion of the vertical distance between the red lines in Fig. 2 that can have functions passing through it with the specified density and slope at x^*.

We can also use optimal control theory to efficiently compute the functional density of points. We first partition the domain by points v_l, $l = 1, \dots, p$, at which we check the range of values $f(v_l)$ can take. For each point v_l, and for a given value f_l, we can check whether f_l can be taken by a valid function satisfying $\left(x^*, f'(x^*)\right)$ and remaining inside our constraints by using the same differential equation $(B1)$, since we are still aiming to optimise the same functional. We just need to include v_l in the partitioning set along with 0, x^* and $x_{\max}$, and specify $y_1(v_l) = f_l$ as a boundary condition at this point. The appropriate boundary conditions can be easily derived based on the general framework in Appendix A. The optimal function $\tilde{f}$ will be the function passing through $\left(x^*, \frac{d}{k}\right)$ with derivative f_1^* and through (v_l, f_l) that best fits our quantitative and qualitative constraints. If $\tilde{f}$ lies within our bounds, then we have found a valid function and the point (v_l, f_l) should count towards the functional density of the point (x^*, f_1^*). Checking this for many different values of f_l, we can work out the entire range of points such a function can pass through at v_l and take the ratio of this range to the total height of the bound at v_l. After we do this for all v_l, we can then take the average of these values to approximate the functional density.

Fig. 5 shows the area that can be covered for two sets of values, (x^*, f_1^*). In Fig. 5A, these values are $x^* = 0.15$, $f_1^* = 1.9$. This point in the generalised bifurcation space is demarked by the cross in Fig.3, and represents a low functional density of 0.3895 whereas in Fig. 5B, the values are $x^* = 0.16$ and $f_1^* = 1.5$, correspond to the circle in Fig.3, and representing a higher functional density, 0.4725. By computing functional densities at different points in the domains in the stability plots in Fig.3, one can more accurately estimate the degree of sensitivity by using the functional density as the weighting ρ in (20).

4. Discussion and conclusions

In this paper we have presented a method for detecting and quantifying structural sensitivity in biological models by formulating them as partially specified models and applying optimal control theory. This method has an advantage over standard parameter-based approaches (e.g. Bendoricchio and Jorgensen, 2001) since it allows us to cover all function relations and not stick to any particular mathematical formulation. Interestingly, even more advanced non-parametric methods in statistics, which take into account constraints on functions, might not be reliable since using two different non-parametric methods can result in rather different predictions (Cadigan, 2013). Partially specified models work by leaving uncertain functions unspecified apart from some local and global qualitative constraints and some error bounds which the functions must pass between. In order to analyse such models in terms of the number of equilibria and their stability, for instance, we can then simply find the isocline equations and the Jacobian matrix as usual: any values which we need for this which are unknown due to the function being unspecified can be considered as parameters in a generalised bifurcation space.

In partially specified models, the constraints on the considered functions are an integral part of the model, and not something to be explored as a supplementary investigation, after the analysis is done. The main approach is to project the set of functions fitting the constraints into the generalised bifurcation space. This is in contrast to the well-known framework of generalised modelling and the analogous structural kinetic modelling (Gross & Feudel, 2006; Steuer et al., 2006; Kuehn et al. 2012). In these frameworks, unknown model functions are also left unspecified and local bifurcation analysis carried out by way of incorporating unknown values into a generalised bifurcation space. However, instead of incorporating the constraints on the functions into the model, and anchoring our generalised bifurcation space to these constraints via a projection, the initial model is transformed so that the generalised bifurcation analysis comes out in terms of general parameters which are more biologically interpretable and measurable than equilibrium densities, etc. However, there is no escaping the fact that all of these generalised parameters will necessarily be values that need to be measured at the equilibrium density itself. With the approach proposed here, considering the whole possible span of functions, this dependence on measurements at a single density vanishes. It is interesting to briefly compare our sensitivity analysis results to those using the generalised modelling approach (see Appendix C for details). We can see that the generalised modelling approach considers a huge range of values of the generalised parameters x^* and $f'(x^*)$, the majority of which will not correspond to any valid function under given constraints, and therefore an analysis based on this approach might be misleading.

The key innovation introduced in this paper concerns how we project the set of valid functions—those satisfying qualitative constraints and staying within certain bounds—into the generalised bifurcation space. To find such a projection in general, we need to determine whether or not a differentiable function f exists satisfying some global constraints on it and its derivatives (2)-(3), as well as being fixed at some points (4). The precise solution of this problem in general is an extremely challenging mathematical endeavour. Here, we construct an approximation to the initial mathematical problem by constructing a functional which penalises functions for breaking the constraints or leaving the area between the bounds, finding the function which maximises it, and checking whether this function satisfies the constraints. This is an optimization problem that can then be solved by standard numerical methods.

In (Adamson and Morozov, 2012) the projection of the set of valid functions into the generalised bifurcation space was done exactly, using a geometric method. This approach is computationally very quick, but requires new calculations by hand for each set of qualitative constraints on functions, and is only valid for error bounds that satisfy these constraints themselves. The optimal control approach presented here is more flexible with regards to the shape of error bounds and qualitative constraints it can handle. In particular, changing the error bounds requires only a small change in the optimal control problem, since the actual shape of the boundary only determines the precise functional we aim to optimise. Since the optimal control approach distils all of the functionals inputted into a boundary value problem to be solved, it opens up the possibility for software to be developed that performs structural sensitivity analysis without a need for extra analytical work by the user.

We should stress here that when building the objective functional (5) we 'soften' the bounds $h^i(x)$ in (2)-(3): functions and their derivatives no longer need to lie between two curves to be valid. However, the use of smoothed step functions in the objective functional mean that we approximate the hard bounds. The framework presented here could be altered by dispensing with bounds completely and replacing the smoothed step functions in the objective functional with Gaussian-type functions. The generalised bifurcation parameters could then be weighted by how the corresponding optimal functions score in the objective functional. This score is obtained automatically through the optimal control approach, and even in the case of approximately hard bounds, it may serve as an alternative weighting to the functional density introduced in section 3.4 without any extra computation required. However, this involves giving full voice to the best fitting function, whereas the functional density considers the range of possible functions taking the given generalised bifurcation values.

A potential misgiving of the approach to sensitivity analysis presented here is that we have demonstrated it on a very simple model: the two-component Rosenzweig-MacArthur predator prey model, where only the functional response is unknown. However, we should stress that we have presented this model for the sake of simplicity. The same method can certainly be applied when multiple functions are unspecified, although we need to consider higher-dimensional domains instead of considering two-dimensional plots such as Figure 3. Such domains would be harder to visualise, but we can still readily compute the probability of having a given type of dynamics by computing the (higher dimensional) volumes of the corresponding regions. Moreover, even if the unknown functions are embedded in complex models containing dozens or hundreds of equations, the analysis presented here stays the same.

There are several existing issues with regards to smooth numerical execution of the method presented here. These issues are related to the difficulty of solving high-dimensional boundary value problems numerically. In particular, more advanced numerical methods would need to be developed for efficiently solving these problems: here we’ve used the simple shooting method (Burden & Faires, 2001), which requires reasonable initial guesses as inputs, and shows slow convergence near the margins of the domain of valid functions in the generalized bifurcation space. Creation of more efficient methods would pay off remarkably, since it would enable the development of software to project unknown functions into generalised bifurcation spaces automatically, without any analytical work needed from the user. This would pave the way towards rigorous, flexible and fully automated structural sensitivity analysis being made available to the entire modelling community.

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Ethics statement. This work did not involve any active collection of any biological data.

Data accessibility statement. This work does not have any experimental data.

Competing interests statement. We have no competing interests.

Authors’ contributions. A.M, M.A. and O.K conceived the sensitivity analysis method, interpreted the computational results. A.M, M.A. wrote the paper. M.A. implemented and performed most of simulations and optimization calculations in consultation with A.M. and O.K. All authors gave final approval for publication.

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Figure Captions

1. Sample plot representing the functions $F_j\left(f^{(j)}(x), x\right)$ defined in (6) to be included in the functional I in (5). At each point x, F_j will be high when the j-th derivative is within its specified bounds, and low when it lies outside them. Therefore, the functions that yield high values when F_j is integrated over all x will be ones that adhere to the restrictions.

2. An example of a valid Holling-type II functional response lying within a complex bounds, as computed as the function optimising I in (16) for given values x^* and $f'(x^*)$, shown in blue. The global bounds on the function values, h^0_{low} and h^0_{high} are shown in red. The values we are checking are shown by dashed lines: x^*, $f(x^*)$ and the tangent line at this point with slope $f'(x^*)$.

3. The region of the generalised bifurcation space—consisting of the prey equilibrium density, x^* and the slope of the functional response at this density, $f'(x^*)$—that corresponds to functional responses satisfying conditions (12)-(15) and remaining within the red bounds in Fig. 2. Dark blue indicates points that lie outside this region. Within the region, green indicates that the Rosenzweig-MacArthur system with such a function will have a stable interior equilibrium, and red indicates it will have an unstable interior equilibrium. The light blue region is that which can be covered by varying parameters of the Monod function while remaining within the same bounds. The cross and circle are the points corresponding to a high and low functional density (see section 3.4), as shown in Fig. 5A and B, respectively. The parameters of the Rosenzweig-MacArthur model are $= 0.1, K = 0.59$, $k = 0.3$, $d = 0.1$.

4. Plot of the dependence of the probability of observing a stable equilibrium (blue curve) and the degree of structural sensitivity (red curve) on the carrying capacity, K. 1 is the highest possible degree of structural sensitivity, at which we have maximum uncertainty of the model dynamics, if the degree of sensitivity is 0 then we have no uncertainty. Explanations of how these are computed are provided in sections 3.2 and 3.3, respectively. All other parameters are the same as in Fig. 3.

5. Computing the functional density of a point $\left(x^*, f'(x^*)\right)$ in generalised bifurcation space. The range of values that can be attained by valid functions passing through x^* at the value $\frac{d}{k}$ with the slope $f'(x^*)$, for two such pairs of values: a) $x^* = 0.15$, $f_1^* = 1.9$—given by the cross in Fig. 3, and corresponding to a functional density of 0.3895, b) $x^* = 0.16$ and $f_1^* = 1.5$—given by the circle in Fig. 3 and corresponding to a functional density of 0.4725.

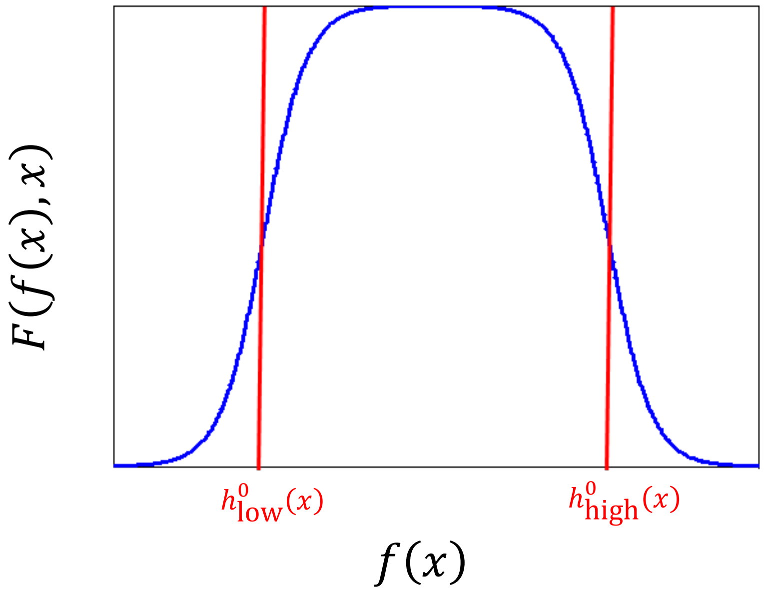
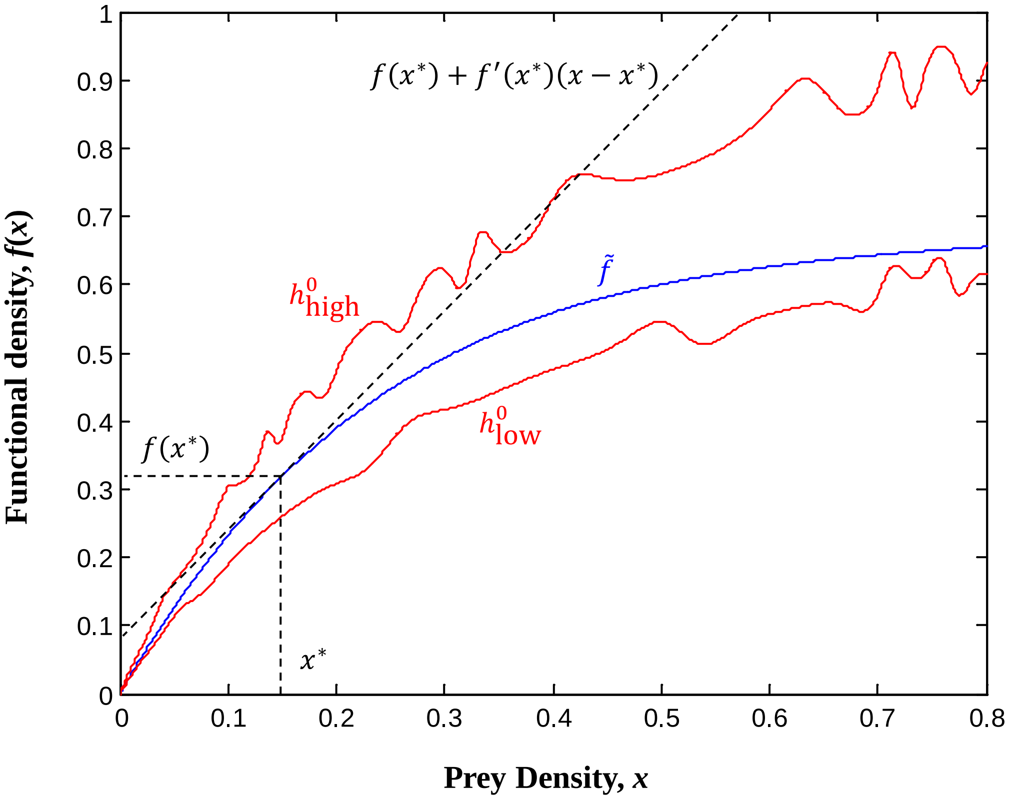


Figure 1



$f(x^*) + f'(x^*)(x - x^*)$
h^0_{high}
$\tilde{f}$
h^0_{low}
$f(x^*)$
x^*
Functional density, $f(x)$
Prey Density, x
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1

Figure 2

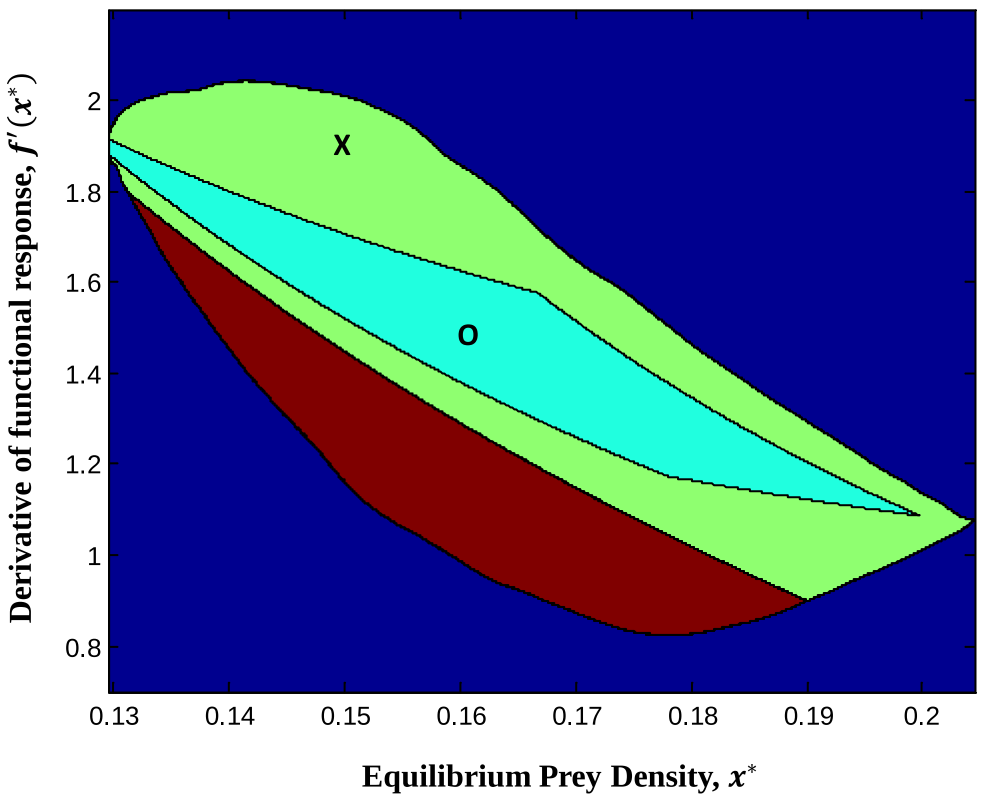

X
O
2
1.8
1.6
1.4
1.2
1
0.8
0.13
0.14
0.15
0.16
0.17
0.18
0.19
0.2
Derivative of functional response, $f'(x^*)$
Equilibrium Prey Density, x^*

Figure 3

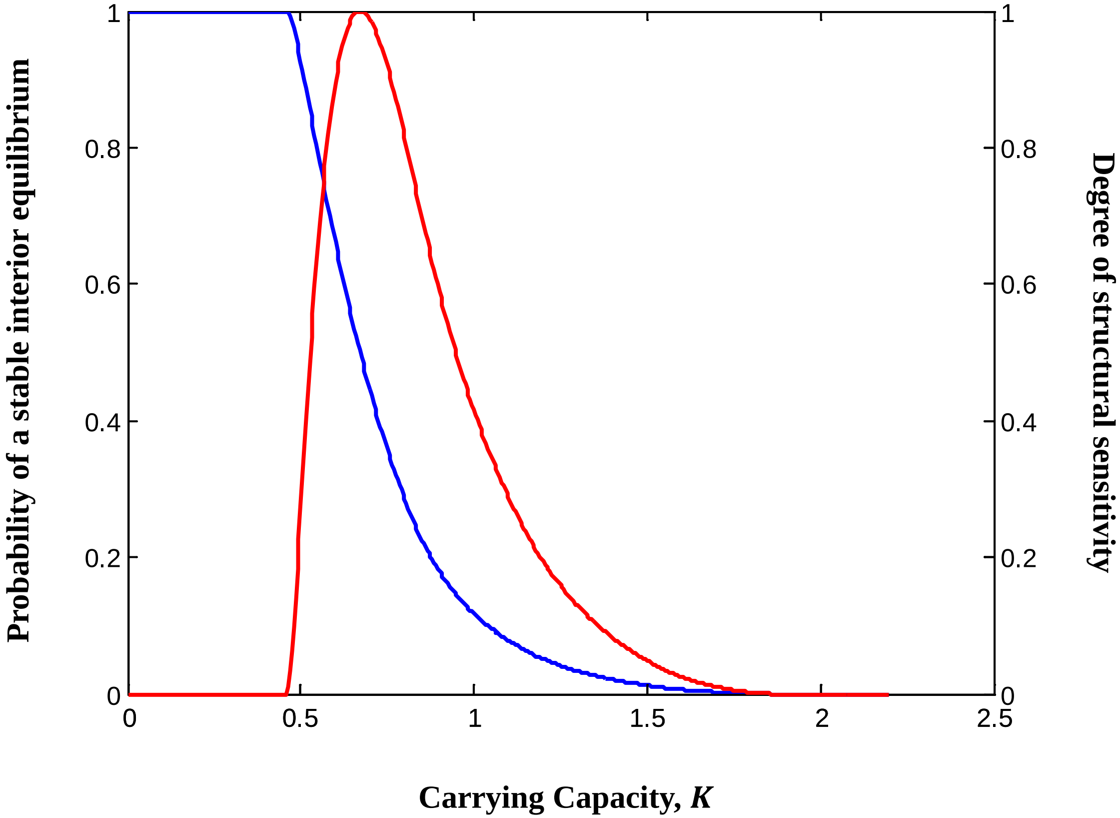
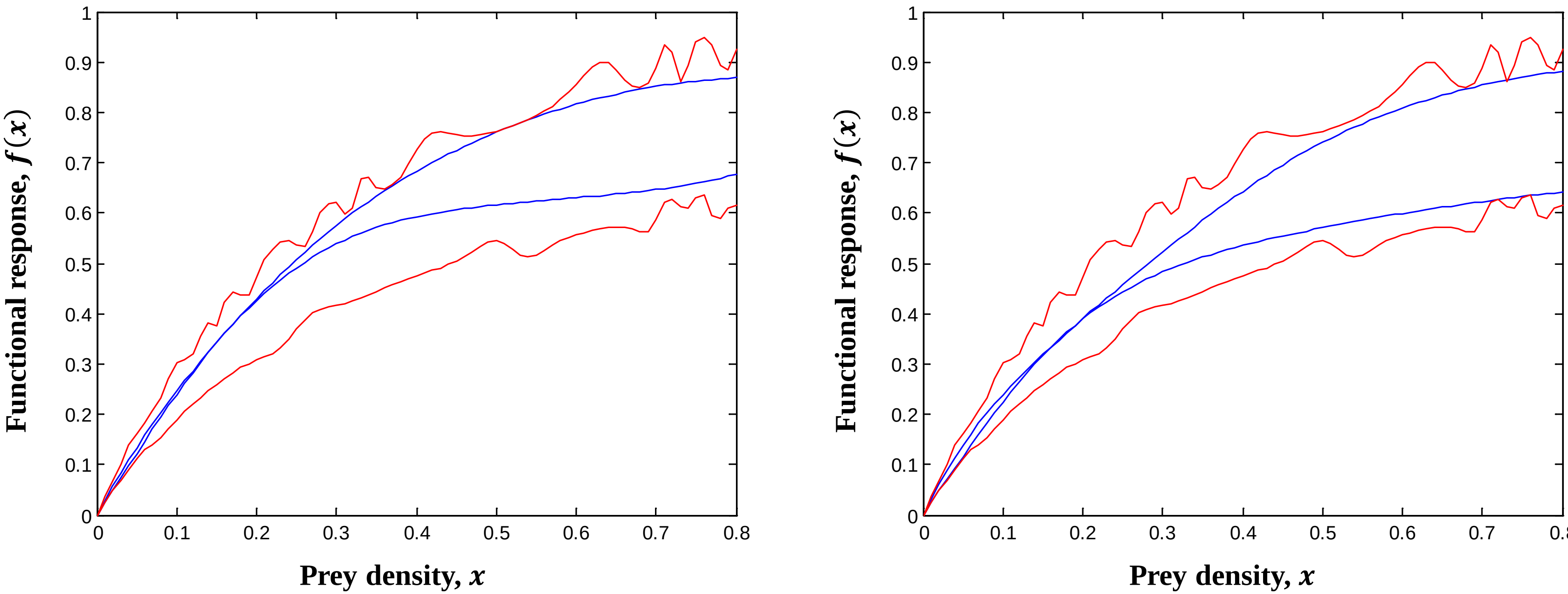

Probability of a stable interior equilibrium
Degree of structural sensitivity
Carrying Capacity, *K*
0
0.2
0.4
0.6
0.8
1
0.5
1.5
2
2.5

Figure 4



Functional response, f(x)
Prey density, x
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Functional response, f(x)
Prey density, x

Figure 5