Defining and Detecting Structural Sensitivity in Biological Models: Developing a New Framework

Matthew Adamson

In collaboration with Andrew Morozov

Department of Mathematics,
University of Leicester, UK
What is structural sensitivity?

• An ODE model is *structurally sensitive* when small changes in the model functions result in substantially different predictions.

• For example: a bifurcation hypersurface may be crossed when the model parameters are varied slightly.

• However, in biological modelling, we are often not sure of the choice of all the functional forms in the first place.
Structural Sensitivity: An Example

A Rosenzweig-MacArthur Model with different Holling-type II functional responses:

\[
\dot{P} = rP \left(1 - \frac{P}{K}\right) - h_i(P) \cdot Z
\]
\[
\dot{Z} = h_i(P) \cdot Z - mZ
\]

\[
h_1(P) = \frac{a_1 \cdot P}{1 + b_1 \cdot P}
\]
\[
h_2(P) = a_2 \cdot \text{atanh}(b_2 \cdot P)
\]
\[
h_3(P) = a_3 \cdot (1 - \exp(-b_3 \cdot P))
\]

‘Community response to enrichment is highly sensitive to model structure’
Fussmann & Blasius, 2005
Structural Sensitivity: An Example

A Rosenzweig-MacArthur Model with different Holling-type II functional responses:

\[ \dot{P} = rP \left(1 - \frac{P}{K}\right) - h_i(P) \cdot Z \]
\[ \dot{Z} = h_i(P) \cdot Z - mZ \]

\[ h_1(P) = \frac{a_1 \cdot P}{1 + b_1 \cdot P} \]
\[ h_2(P) = a_2 \cdot \text{atanh}(b_2 \cdot P) \]
\[ h_3(P) = a_3 \cdot (1 - \exp(-b_3 \cdot P)) \]

‘Community response to enrichment is highly sensitive to model structure’
Fussmann & Blasius, 2005
Overview

In this talk, we are going to:

• Define structural sensitivity, and discuss several definitions of the ‘distance’ between two models.

• Develop an intensive method for detecting some cases of structural sensitivity in ODE models.

• Use this method to investigate structural sensitivity in some biological models.

• Discuss the implications of structural sensitivity for ecological modelling.
Structural Stability

Definition (*Strict structural stability*):

Consider a continuous-time dynamical system:

\[ \dot{x} = f(x), \quad x \in \mathbb{R}^n \]  

(1)

with smooth \( f \), defined over a closed region \( \Omega \subset \mathbb{R}^n \).

System (1) is *strictly structurally stable* over \( \Omega \) if any system that is sufficiently \( C^1 \)-close in \( U \) is topologically equivalent to (1).

Where two systems are *topologically equivalent* if there is a continuous bijection with continuous inverse mapping the (directed) orbits of one system to those of the other.
Structural Sensitivity: General Definition

We denote by $B_\varepsilon(M_R)$ the set of models $(M)$ such that $d(M_R, M) < \varepsilon$.

For an initial condition $x \in \mathbb{R}^n$, we denote by $\omega_R(x)$ its $\omega$-limit with the model $(M_R)$ and by $\omega(x)$ its $\omega$-limit with the model $(M)$.

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

(i) $(M)$ is not structurally stable;

(ii) there exists a set $X \subseteq \mathbb{R}^n$ of positive measure, such that given any initial condition $x \in X$, we have $d_H(\omega_R(x), \omega(x)) \geq \sigma$ ($d_H$ the Hausdorff distance).
Defining distance between models: The $C^1$-metric

Consider two continuous-time systems:

\[
\dot{x} = f(x), \text{ and } \dot{x} = g(x), \quad x \in \mathbb{R}^n,
\]

with $f$ and $g$ being $C^1$ vector fields on $\mathbb{R}^n$. The $C^1$-distance between systems (3) and (4) is the positive number given by:

\[
\sup_{x \in \Omega} \left\{ \| f(x) - g(x) \| + \left\| \frac{df(x)}{dx} - \frac{dg(x)}{dx} \right\| \right\}
\]

where $\| f(x) - g(x) \|$ is a vector norm and $\left\| \frac{df(x)}{dx} - \frac{dg(x)}{dx} \right\|$ is a matrix norm over $\mathbb{R}^n$. 
Defining distance between models: Parameter variation

Given two systems:
\[ \dot{x} = f(x, \alpha_1, \ldots, \alpha_m) \quad \text{and} \quad \dot{x} = f(x, \hat{\alpha}_1, \ldots, \hat{\alpha}_m), \]
where \( x \in \mathbb{R}^n, \ \alpha_i, \hat{\alpha}_i \in \mathbb{R}. \)

The \textit{parameter variation distance} between them over a closed region \( \Omega \subseteq \mathbb{R}^n \) is the positive number given by:
\[ \sup_{x \in \Omega} \| f(x, \alpha_1, \ldots, \alpha_m) - f(x, \hat{\alpha}_1, \ldots, \hat{\alpha}_m) \|, \]
where \( \| \cdot \| \) denotes a vector norm in \( \mathbb{R}^n. \)

But this requires us to know the functional form in the first place!
Defining distance between models: 

The absolute $d_Q$-distance

Consider two continuous-time systems:

\[ \dot{x} = G(g_1(x), \ldots, g_m(x), h_1(x), \ldots, h_p(x)), \quad x \in \mathbb{R}^n, \]

and

\[ \dot{x} = G(g_1(x), \ldots, g_m(x), \tilde{h}_1(x), \ldots, \tilde{h}_p(x)), \quad x \in \mathbb{R}^n, \]

where $g_1, \ldots, g_m \in C^1(\mathbb{R}^n)$, and $h_1, \ldots, h_p, \tilde{h}_1, \ldots, \tilde{h}_p \in Q$ where $Q \subseteq C^1(\mathbb{R}^n)$ is a class of functions satisfying certain specific conditions, including bounded second derivatives.

The absolute $d_Q$-distance between them over a closed region $\Omega \subseteq \mathbb{R}^n$ is the positive number given by:

\[
d_Q := \sup_{x \in \Omega} \sqrt{\left(\|h_1(x) - \tilde{h}_1(x)\|\right)^2 + \cdots + \left(\|h_p(x) - \tilde{h}_p(x)\|\right)^2}.
\]
Defining distance between models:
The relative $d_Q$-distance

Consider the same two systems as before:

$$\dot{x} = G\left(g_1(x), \ldots, g_m(x), h_1(x), \ldots, h_p(x)\right), \quad x \in \mathbb{R}^n,$$

and

$$\dot{x} = G\left(g_1(x), \ldots, g_m(x), \tilde{h}_1(x), \ldots, \tilde{h}_p(x)\right), \quad x \in \mathbb{R}^n.$$

The **relative $d_Q$-distance** between them over a closed region $\Omega \subseteq \mathbb{R}^n$ is the positive number given by:

$$d_Q := \sup_{x \in \Omega} \sqrt{\frac{\left(\|h_1(x) - \tilde{h}_1(x)\|\right)^2 + \cdots + \left(\|h_p(x) - \tilde{h}_p(x)\|\right)^2}{\max\{h_1(x)^2 + \cdots + h_p(x)^2, \tilde{h}_1(x)^2 + \cdots + \tilde{h}_p(x)^2\}}}.$$
Advantages of the $d_Q$-distance

- We can ensure that we only consider biologically relevant models by our choice of the class of functions $Q$.
- Allows the forms of model functions to vary.
- Can be directly related to errors in data measurement.
\( \varepsilon_Q \)-neighbourhoods and experimental error

The definition of the \( d_Q \) distances gives rise to neighbourhoods of models—the set of models within a distance \( \varepsilon \) of the original. If \( \varepsilon \) is an experimental error, the \( \varepsilon_Q \)-neighbourhood will be the set of model functions which fit the data given by the ‘base function’.
Structural Sensitivity: General Definition

We denote by $B_\varepsilon(M_R)$ the set of models $(M)$ such that $d(M_R, M) < \varepsilon$.

For an initial condition $x \in \mathbb{R}^n$, we denote by $\omega_R(x)$ its $\omega$-limit with the model $(M_R)$ and by $\omega(x)$ its $\omega$-limit with the model $(M)$.

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

(i) $(M)$ is not structurally stable;

(ii) there exists a set $X \subseteq \mathbb{R}^n$ of positive measure, such that given any initial condition $x \in X$, we have $d_H(\omega_R(x), \omega(x)) \geq \sigma$ ($d_H$ the Hausdorff distance).
We consider a model

\[ \dot{x} = G(g_1(x), ..., g_m(x), \tilde{h}(x)), \quad x \in \Omega \subset \mathbb{R}^n \]

where \( g_1, ..., g_m \) are known real valued functions and \( \tilde{h}: \Omega \to \mathbb{R} \) a function in \( Q \) with unknown formulation. We make an initial choice of base function \( h \) from \( Q \). This should be fitted to experimental data if possible.

Can the stability of a given equilibrium \( x^* \) change if \( h \) is replaced with another function from its \( \epsilon_Q \)-neighbourhood?
General Framework

• It’s clearly impossible to cover all functions in the \( \varepsilon_Q \)-neighbourhood – it is infinite dimensional.

• However, with respect to some properties (e.g. stability of equilibria), the only values we need to know are the equilibrium points, and the values taken by the unknown function and its derivative at the equilibria.

• So we project the \( \varepsilon_Q \) – neighbourhood from infinite dimensional function space into a finite dimensional space of these values.
Projection from function space (infinite dimensional) to a space of local values

• Given values \((x^*, \tilde{h}(x^*), \tilde{h}'(x^*))\), we want to find the necessary and sufficient conditions for them to correspond to a function \(\tilde{h}\) in the \(\varepsilon_Q\)–neighbourhood of \(h\).

• This is a nonlocal problem, since we require functions to be within a distance \(\varepsilon\) from the base function at all points in the domain.
Demonstration: The Rosenzweig-MacArthur Predator-Prey Model

\[ \dot{P} = r \left( 1 - \frac{P}{K} \right) \cdot P - \tilde{h}(P) \cdot Z, \]
\[ \dot{Z} = k \cdot \tilde{h}(P) \cdot Z - m \cdot Z, \]

- \( P \) is the prey density, \( Z \) is the predator/consumer density.
- \( \tilde{h} \) is the functional response of the predator (Holling type II).

Therefore, we define our function class \( Q \) as follows:

\[ Q := \{ \tilde{h} \in C^1(\mathbb{R}) | \tilde{h}(0) = 0; \tilde{h}'(P) > 0 \text{ and } A < \tilde{h}''(P) < 0 \quad \forall \ P \in [0, P_{\text{max}}] \}. \]

Further we note that the isoclines yield \( \tilde{h}(P^*) = \frac{m}{k} \) at any interior equilibrium. Therefore we only need to vary \( P^* \) and \( \tilde{h}'(P^*) \) in our investigation.
Finding the Projection: Holling Type II Case

Given the values $P^*$ and $\tilde{h}'(P^*)$, then any function with curve passing through $\left( P^*, \frac{m}{k} \right)$ with slope $\tilde{h}'(P^*)$ has the following bounds, since $A < \tilde{h}''(P) < 0$:

**Theorem:**
If the upper bound lies above $h_{\varepsilon-}$ and the origin, and the lower bound lies below $h_{\varepsilon+}$ and the origin, then there is a function at this point in the $\varepsilon$-neighbourhood.
Base Functions

We shall use two base functions in this example:

\[ h_1(P) = a_1 \frac{P}{1 + b_1 P} \]
\[ h_2(P) = a_2 \tanh(b_2 P) \]

with \( a_1, b_1, a_2 \) and \( b_2 \) chosen so that the two functions are close.

This way we can ensure our test is consistent: we don’t want our test for structural sensitivity to be sensitive itself!
Stability Portraits of the $\varepsilon_Q$-neighbourhood: $K=0.6$

**Green domain**: the system with such functions will be stable

**Red domain**: the system with such functions will be unstable

**Azure domain**: the area which can be covered by varying the parameters of the base function
The Variation of Parameters Approach: A Blinkered Horse?

No sensitivity here!
Stability Portraits of the $\varepsilon_Q$-neighbourhood: $K=0.6$

Green domain: the system with such functions will be stable
Red domain: the system with such functions will be unstable
Azure domain: the area which can be covered by varying the parameters of the base function
Stability Portraits of the $\varepsilon_Q$-neighbourhood: $K=1.2$

**Monod Base Function**

**Hyperbolic Tangent Base Function**

**Green domain:** the system with such functions will be stable

**Red domain:** the system with such functions will be unstable

**Azure domain:** the area which can be covered by varying the parameters of the base function
We define the ‘degree’ of structural sensitivity in the system as

\[ \Delta := 4 \cdot \frac{V_1}{V} \cdot \left(1 - \frac{V_1}{V}\right) \]

where \( V_1 \) is the area/volume of the domain of stability, and \( V \) is the total area/volume of the \( \varepsilon_Q \)-neighbourhood.

This is related to the ‘probability’ of two randomly chosen functions yielding different predictions for the stability of \( x^* \).
The Degree of Structural Sensitivity and Probabilities

Assuming that functions are uniformly distributed across our finite-dimensional space of local values, the probability of two randomly chosen functions yielding different stability conditions will be:

\[
2 \cdot \frac{V_1}{V} \cdot \left(1 - \frac{V_1}{V}\right)
\]

If the functions follow some probability density function \( \rho \), then

\[
\Delta := 4 \cdot \frac{\int_{V_1} \rho \, dV}{\int_{V_\varepsilon} \rho \, dV} \cdot \left(1 - \frac{\int_{V_1} \rho \, dV}{\int_{V_\varepsilon} \rho \, dV}\right)
\]

**Green domain:** the system with such functions will be stable

**Red domain:** the system with such functions will be unstable
Dependence of the Degree of Structural Sensitivity on $K$: Absolute Error

There is structural sensitivity in the system for a large range of $K$.

The results of the analysis do not depend strongly upon the choice of base function.

Blue lines: Monod base function used
Red lines: Hyperbolic tangent base function used
Green line: Sensitivity threshold
Dependence of the Degree of Structural Sensitivity on $K$: Relative Error

The results of the analysis do appear to depend on the choice of base function!

However, when $\varepsilon=0.7$, the results are more similar.

Blue lines: Monod base function used
Red lines: Hyperbolic tangent base function used
Green line: Sensitivity threshold
Dependence of the Degree of Structural Sensitivity on $K$: Relative Error

The results of the analysis do appear to depend on the choice of base function!

However, when $\varepsilon=0.7$, the results are more similar.

Blue lines: Monod base function used
Red lines: Hyperbolic tangent base function used
Green line: Sensitivity threshold
But Recall the Base Functions:

The relative $d_Q$-distance between them is quite large!
Dependence of the Degree of Structural Sensitivity on $K$: Relative Error

The results of the analysis do appear to depend on the choice of base function!

However, when $\varepsilon=0.7$, the results are more similar.

Blue lines: Monod base function used
Red lines: Hyperbolic tangent base function used
Green line: Sensitivity threshold
The General Rosenzweig-MacArthur Predator-Prey Model

\[ \dot{P} = \tilde{r}(P) \cdot P - \tilde{h}(P) \cdot Z, \]
\[ \dot{Z} = k \cdot \tilde{h}(P) \cdot Z - m \cdot Z, \]

- \(P\) is the prey density, \(Z\) is the predator/consumer density.
- \(\tilde{h}\) is the functional response of the predator (Holling type II).
- \(\tilde{r}\) is the prey growth rate (Logistic-type)

Next, let’s investigate structural sensitivity of the system with respect to \(\tilde{r}\).
We shall let the functional response \(\tilde{h}\) take either the Monod or Hyperbolic tangent form.
Variation of the Prey Growth Function

Logistic-type prey growth functions must satisfy the following conditions:

\[ \tilde{r}'(P) < 0 \quad \text{and} \quad A_1 < \tilde{r}''(P) < A_2 \quad \forall P \in [0, P_{\text{max}}], \]

where \( A_1 \in (-\infty, 0] \) and \( A_2 \in [0, \infty) \).

We shall use the standard logistic function as the base function in this example:

\[ r(P) = r \cdot \left(1 - \frac{P}{K}\right) \]
Stability Portraits of the $\varepsilon_Q$-neighbourhood: Varying growth function with Monod functional response

$K=0.65$

$K=0.8$

**Green domain:** the system with such functions will be stable

**Red domain:** the system with such functions will be unstable

**Azure domain:** the area which can be covered by varying the parameters of the base function
Stability Portraits of the $\varepsilon_Q$-neighbourhood: Varying growth function with Hyperbolic tangent functional response

**Green domain:** the system with such functions will be stable

**Red domain:** the system with such functions will be unstable

**Azure domain:** the area which can be covered by varying the parameters of the base function
Dependence of the Degree of Structural Sensitivity on $K$: Absolute Error

The degree of structural sensitivity with respect to the growth function depends heavily on the functional response of the predator!

Blue lines: Monod base function used
Red lines: Hyperbolic tangent base function used
Green line: Sensitivity threshold
Extension of the Degree of Structural Sensitivity: Functional Density

We can assign a measure of ‘importance’ of a point in the space of local values by considering the volumes of points on the graph which functions taking those values can pass through.
Sample Functional Density Portraits

Monod functional response, $K=0.8$

Hyperbolic tangent functional response, $K=2$

Value of the prey growth rate $r(P^*)$

Derivative of growth function, $r'(P^*)$
Age-structured Predator-prey model in a chemostat with nutrient

\[
\begin{align*}
\frac{dN}{dt} &= \delta(N_i - N) - \tilde{h}(N)C, \\
\frac{dC}{dt} &= \tilde{h}(N)C - \frac{1}{\varepsilon} \cdot \frac{b_B C}{K_B + C} B - \delta C, \\
\frac{dR}{dt} &= \frac{b_B C}{K_B + C} R - (\delta + m + \lambda)R, \\
\frac{dB}{dt} &= \frac{b_B C}{K_B + C} R - (\delta + m)B,
\end{align*}
\]

\(N\) is the nutrient concentration, \(C\) is the concentration of algae, \(R\) is the concentration of herbivores of reproductive age, and \(B\) is the total concentration of herbivores.

(Fussmann, Ellner, Shertzer & Hairston Jr., 2001)

We can investigate the structural sensitivity of the system with respect to variation of the Holling type II functional response.
Stability Portraits of the $\varepsilon_Q$-neighbourhood: 4-dimensional Chemostat Model

Predation of zooplankton, $d=1$


Predation of zooplankton, $d=1.7$


**Green domain**: the system with such functions will be stable  
**Red domain**: the system with such functions will be unstable  
**Azure domain**: the area which can be covered by varying the parameters of the base function
4-Dimensional Nutrient-Phytoplankton-Zooplankton-Detritus Model

\[
\begin{align*}
\frac{dN}{dt} &= -\frac{N}{(e+N)(b+cP)} \frac{a}{P} P + \beta \frac{\lambda P^2}{\mu^2 + P^2} Z + \gamma dZ^2 + \phi D + k(N_0 - N), \\
\frac{dP}{dt} &= \frac{N}{(e+N)(b+cP)} \frac{a}{P} P - rP - \frac{\lambda P^2}{\mu^2 + P^2} Z - (s+k)P, \\
\frac{dZ}{dt} &= \alpha \frac{\lambda P^2}{\mu^2 + P^2} Z - dZ^2, \\
\frac{dD}{dt} &= rP + (1-\alpha-\beta) \frac{\lambda P^2}{\mu^2 + P^2} Z - (\phi + \psi + k)D,
\end{align*}
\]

(Edwards, 2001)

\(N\) is a nutrient; \(P\) is the concentration of phytoplankton; \(Z\) is the concentration of zooplankton, and \(D\) is the concentration of detritus.

We investigate the structural sensitivity of the system with respect to variation of the sigmoid functional response.
4-Dimensional Nutrient-Phytoplankton-Zooplankton-Detritus Model

\[
\frac{dN}{dt} = -\frac{N}{(e + N)(b + cP)} \frac{a}{(e + N)(b + cP)} \left( P + \beta \cdot \tilde{h}(P)Z + \gamma dZ^2 + \phi D + k(N_0 - N) \right),
\]

\[
\frac{dP}{dt} = \frac{N}{(e + N)(b + cP)} \frac{a}{(e + N)(b + cP)} \left( P - rP - \tilde{h}(P)Z - (s + k)P \right),
\]

\[
\frac{dZ}{dt} = \alpha \cdot \tilde{h}(P)Z - dZ^2,
\]

\[
\frac{dD}{dt} = rP + (1 - \alpha - \beta) \tilde{h}(P)Z - (\phi + \psi + k)D,
\]

(Edwards, 2001)

\(N\) is a nutrient; \(P\) is the concentration of phytoplankton; \(Z\) is the concentration of zooplankton, and \(D\) is the concentration of detritus.

We investigate the structural sensitivity of the system with respect to variation of the sigmoid functional response.
Finding the Projection: General Inflection Case

In the case that we have $n$ inflection points, we can extend the previous theorem similarly. The main difference is that we need to define the upper and lower bound functions in a piece-wise way.
Stability Portraits of the $\epsilon_Q$-neighbourhood: 4-dimensional NPZD Model

Predation of zooplankton, $d=1$

Predation of zooplankton, $d=1.7$

**Green domain**: the system with such functions will be stable

**Red domain**: the system with such functions will be unstable

**Azure domain**: the area which can be covered by varying the parameters of the base function
Tri-trophic Food Chain Model with Time-Delay

\[
\frac{dx_1(t)}{dt} = x_1(t)(1 - x_1(t)) - ax_1(t)x_2(t),
\]

\[
\frac{dx_2(t)}{dt} = -bx_2(t) + cx_1(t - \tau)x_2(t) - \tilde{h}(x_2(t))x_3(t) - jx_2(t)^2,
\]

\[
\frac{dx_3(t)}{dt} = -fx_3(t) + k\tilde{h}(x_2(t - \tau))x_3(t) - hx_3(t)^2,
\]

- \(x_1, x_2 \) and \(x_3\) correspond to three consecutive trophic levels, e.g. prey, predator and super-predator.
- \(\tilde{h}\) is a Holling type-II functional response.
- Even though the linear stability analysis for a system of delay-differential equations is more complicated, our approach still works.
Stability Portraits of the $\varepsilon_Q$-neighbourhood: Tri-trophic DDE Model

Time Delay, $\tau=0.5$

Green domain: the system with such functions will be stable
Red domain: the system with such functions will be unstable
Azure domain: the area which can be covered by varying the parameters of the base function
What to do in the case we find structural sensitivity in a system?

- If experimental/field observations remain fairly constant, structural sensitivity may be an indication that something is wrong with the model.
- The logical next step should be to look at experimental data to find the behaviour of the biological system, and choose model functions to replicate this.
- However, because of ‘functional drift’, this may not work, even if we can do this – the results may be completely different next time.
Structural Sensitivity and Irregular Oscillations in Nature

• Processes in real ecosystems will not remain constant.
• The ‘ideal’ mathematical model will change as these processes do.
• In a structurally sensitive model, this may produce irregular oscillations.
• This may help explain the irregular oscillations observed in nature.
Conclusions

• We have presented a rigorous method for detecting structural sensitivity in a system with regards to changes in the stability of an equilibrium.

• Varying parameters of a fixed functional form only gives us a ‘blinker ed horse’ analysis which can be misleading.

• Structural sensitivity is present in many models: it is not an ‘exotic’ phenomenon.

• Structural Sensitivity may offer a possible explanation for the irregular oscillations often observed in nature.
Future Work

• Extend the method so that it can detect **quantitative changes** in systems as well as qualitative ones.

• For example, finding a way to detect changes in the **amplitude of limit cycles**.

• Test the hypothesis that structural sensitivity can exhibit itself as **irregular oscillations in systems**.
Thanks for listening!

Any comments or questions?