The Sensitivity Analysis and Parameter Estimation of Mathematical Models Described by Differential Equations

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(*part of my PhD thesis under the supervision of professor Wayne Enright*)

Outline

- Modeling with Differential Equations (IVPs, DDEs)
- Sensitivity Analysis of Models Described by DEs
- Parameter Estimation of Models Described by DEs

Modeling with DE - Formulation

- An Initial Value Problem (IVP) for Ordinary Differential Equations (ODEs)

$$\begin{aligned} y'(t) &= f(t, y(t)) \\ y(t_0) &= y_0 \end{aligned}$$

- Retarded Delay Differential Equations (RDDEs)

$$\begin{aligned} y'(t) &= f(t, y(t), y(t-\sigma_1), \cdots, y(t-\sigma_\nu)) \ \text{ for } \ t_0 \leq t \leq t_F \\ y(t) &= \phi(t), \ \text{ for } \ t \leq t_0 \end{aligned}$$

$\sigma_i = \sigma_i(t, y(t)) \geq 0$ *delay* (constant / time dependent / state dependent)

$\phi(t)$ *history* function (constant / time dependent)

- Neutral Delay Differential Equations (NDDEs)

$$\begin{aligned} y'(t) &= f(t, y(t), y(t-\sigma_1), \cdots, y(t-\sigma_\nu), \\ &\qquad y'(t-\sigma_{\nu+1}), \cdots, y'(t-\sigma_{\nu+\omega})) \ \text{ for } \ t_0 \leq t \leq t_F \\ y(t) &= \phi(t), \ \ y'(t) = \phi'(t), \ \text{ for } \ t \leq t_0, \end{aligned}$$

Modeling with DE - Some Areas of Application

Area	Example
Ecology	predator-prey
Epidemiology	spread of infections
Immunology	immune response models
HIV infection	
Physiology	human respiration system
Neural Networks	
Cell Kinetics	
Chemical Kinetics	The Oregonator
Physics	Ring Cavity Lasers , two-body problem of electrodynamics

Modeling with DE - An Example

- A neutral delay logistic Gause-type predator-prey system [Kuang 1991]

$$
\begin{aligned}
y_1'(t) &= y_1(t)(1 - y_1(t-\tau) - \rho y_1'(t-\tau)) - \frac{y_2(t)y_1(t)^2}{y_1(t)^2+1} \\
y_2'(t) &= y_2(t)\left(\frac{y_1(t)^2}{y_1(t)^2+1} - \alpha\right)
\end{aligned}
$$

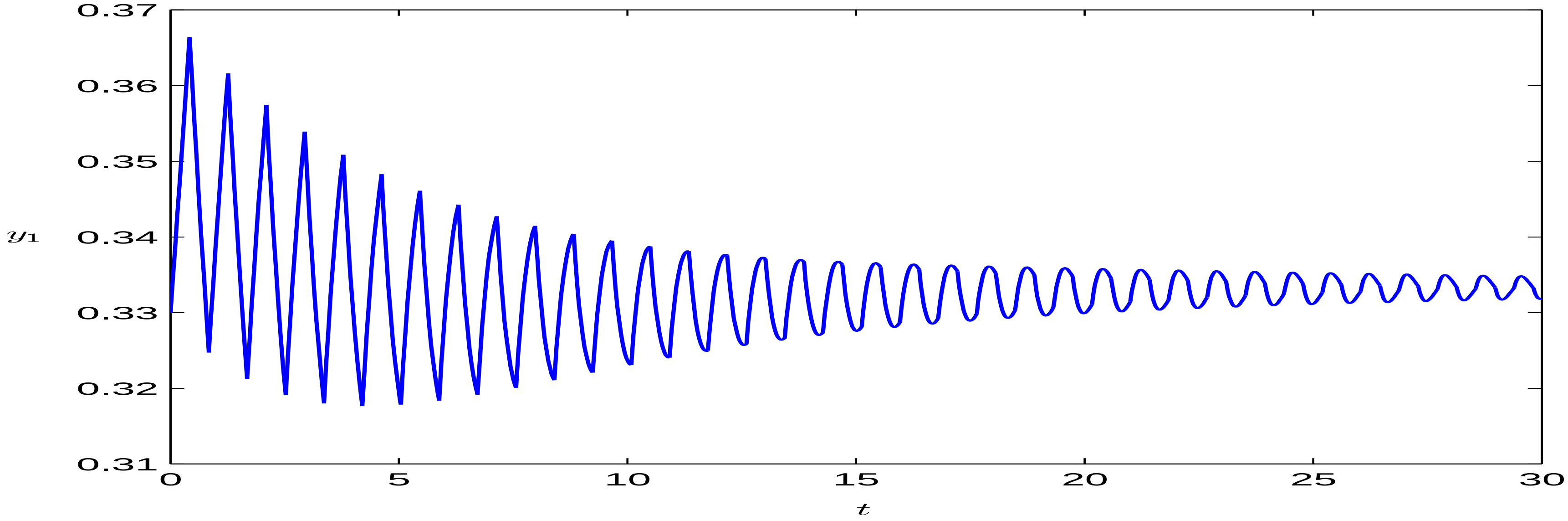
where $\alpha = 1/10$, $\rho = 29/10$ and $\tau = 21/50$, for t in $[0, 30]$. The history functions are

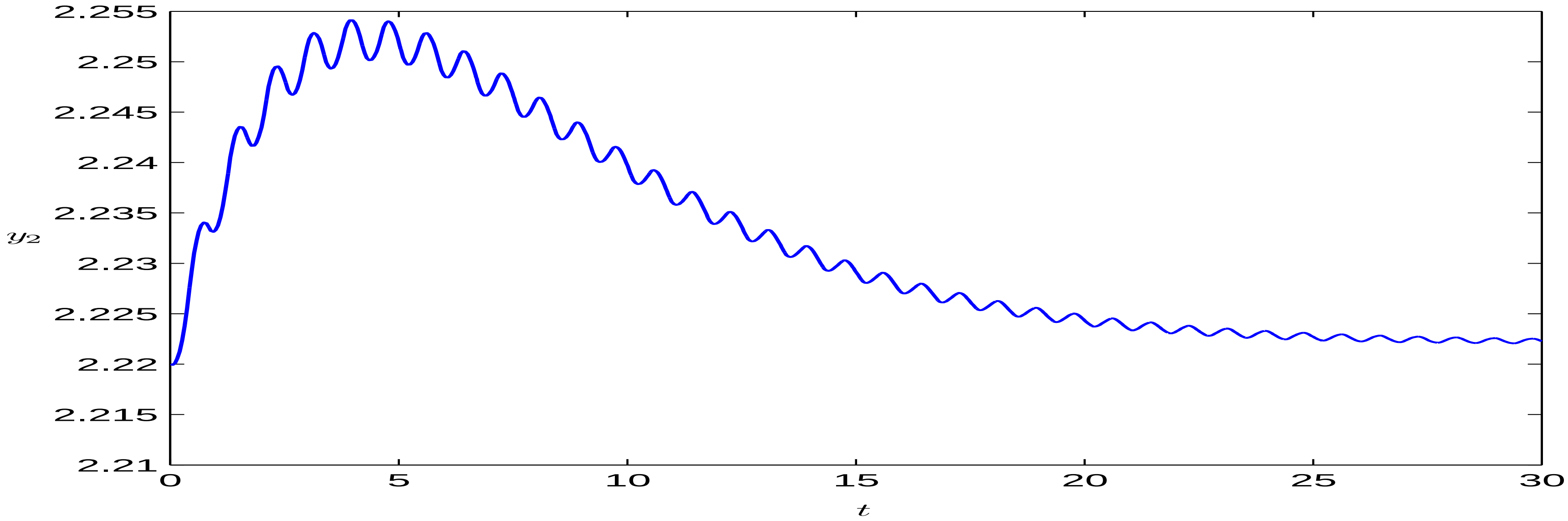
$$
\begin{aligned}
\phi_1(t) &= \frac{33}{100} - \frac{1}{10}t \\
\phi_2(t) &= \frac{111}{50} + \frac{1}{10}t
\end{aligned}
$$

for $t \le 0$.

Modeling with DE - An Example

- The predator-prey model





Modeling with DE - Numerical Simulation

- Classical Theory of Step by Step Integration for IVPs.
  - Runge-Kutta (RK).
  - Linear Multistep (LM).

$$+$$

- Continuous Solution using Polynomial Approximation.
  - Continuous Runge-Kutta (CRK).
  - Linear Multistep methods have natural approximating polynomials.

$$\Downarrow$$

- **DDEs** : Combining an “interpolation” method (for evaluating delayed solution values) with an ODE integration method (for solving the resulting “ODE”).

Modeling with DE - Special Difficulties with DDEs

- Derivative Discontinuities

  In general

$$\phi'(t_0) \neq f(t_0, \phi(t_0), \phi(t_0 - \sigma_1), \cdots, \phi(t_0 - \sigma_\nu))$$

  Due to the existence of *delays*, discontinuities propagate along the integration interval.

  Solution is smoothed for RDDEs but in general not for NDDEs.

  The RK and LM methods fail in presence of discontinuities.

  Treatment : Tracking Discontinuities and forcing them to be mesh points.

Modeling and Sensitivity Analysis - Definitions

- Parameterized Models
  - A parameterized IVP

$$
\begin{aligned}
y'(t;\mathbf{p}) &= f(t, y(t;\mathbf{p});\mathbf{p}) \\
y(t_0) &= y_0(\mathbf{p})
\end{aligned}
$$

For example $\mathbf{p} = [\mu]$ in the Van der Pol oscillator

$$
\begin{aligned}
y_1'(t) &= y_2(t) \\
y_2'(t) &= \mu(1 - y_1^2)y_2 - y_1
\end{aligned}
$$

  - A simple parameterized DDE

$$
\begin{aligned}
y'(t;\mathbf{p}) &= f(t, y(t;\mathbf{p}), y(t - \sigma(t;\mathbf{p}));\mathbf{p}) \quad \text{for} \quad t_0(\mathbf{p}) \le t \\
y(t;\mathbf{p}) &= \phi(t;\mathbf{p}), \quad \text{for} \quad t \le t_0(\mathbf{p})
\end{aligned}
$$

Modeling and Sensitivity Analysis - Definitions

- Forward Sensitivity Analysis
  - The (first order) solution sensitivity with respect to the model parameter p_i is defined as the vector

$$s_i(t;\mathbf{p}) = \{\frac{\partial}{\partial p_i}\} y(t;\mathbf{p}), \quad (i = 1, \ldots, \mathcal{L})$$

  - The second order solution sensitivity with respect to the model parameters p_i and p_j is defined as the vector

$$r_{ij}(t;\mathbf{p}) = \{\frac{\partial}{\partial p_j}\} s_i(t;\mathbf{p}) = \{\frac{\partial^2}{\partial p_j \partial p_i}\} y(t;\mathbf{p}), \quad (i, j = 1, \ldots, \mathcal{L})$$

Modeling and Sensitivity Analysis - Importance

Sensitivity information can be used to:

- Estimate which parameters are most influential in affecting the behavior of the simulation. Such information is crucial for
  - Experimental Design
  - Data Assimilation
  - Reduction of complex nonlinear models
- Study of Dynamical Systems : Periodic orbits, the Lyapunov exponents, chaos indicators, and bifurcation analysis are fundamental objects for the complete study of a dynamical system, and they require computation of the sensitivities with respect to the initial conditions of the problem.
- Evaluate optimization gradients and Jacobians in the setting of
  - Dynamic Optimization
  - Parameter Estimation

Numerical Sensitivity Analysis of IVPs - Forward

- Finite Difference Approach

$$\{\frac{\partial}{\partial p_i}\}y(t;\mathbf{p}) \approx \frac{y(t;\mathbf{p}+\mathbf{e}_i\Delta p_i) - y(t;\mathbf{p})}{\Delta p_i}$$

  Due to the rounding errors, the approximation is only $\mathcal{O}(\sqrt{Tol})$ with the best choice for Δp_i.

- Internal Differentiation

$$y'(t;\mathbf{p}) = f(t, y(t;\mathbf{p});\mathbf{p}), \quad y(t_0) = y_0(\mathbf{p})$$

$$\Downarrow$$

Differentiation + Chain Rule + Clairaut's Theorem

$$\Downarrow$$

$$s_i' = \frac{\partial f}{\partial y}s_i + \frac{\partial f}{\partial p_i}, \quad s_i(t_0) = \frac{\partial y_0(\mathbf{p})}{\partial p_i}, \qquad (i = 1, \ldots \mathcal{L})$$

- Taylor Series method using extended rules of AD [Barrio 2006].
  $\Rightarrow$ second(or higher)-order sensitivities.

Numerical Sensitivity Analysis of IVPs - An Example

- The Van der Pol oscillator

$$
\begin{aligned}
y_1'(t) &= y_2(t) \\
y_2'(t) &= \mu(1 - y_1^2)y_2 - y_1
\end{aligned}
$$

$$\Downarrow$$

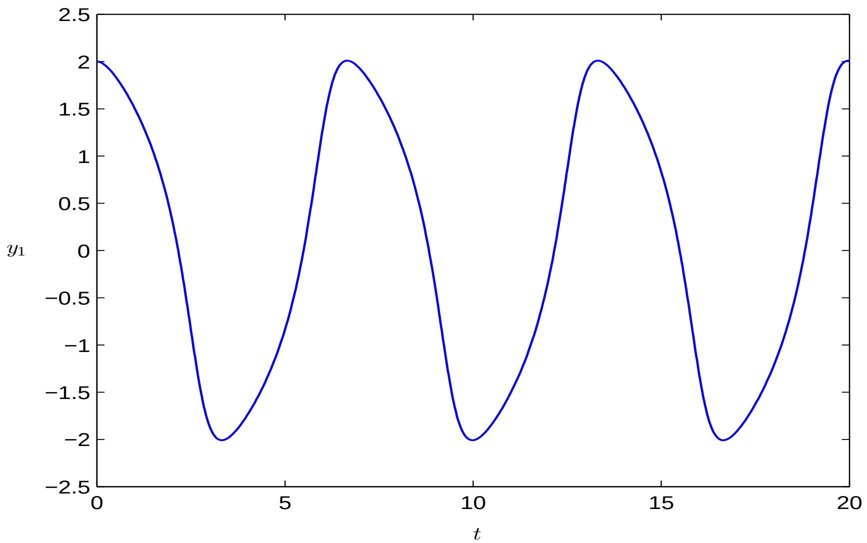
$$
\begin{pmatrix} s'_{1_{(1)}}(t) \\ s'_{1_{(2)}}(t) \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ -2\mu y_1 y_2 - 1 & \mu(1 - y_1^2) \end{pmatrix} \begin{pmatrix} s_{1_{(1)}} \\ s_{1_{(2)}} \end{pmatrix} + \begin{pmatrix} 0 \\ (1 - y_1^2)y_2 \end{pmatrix}
$$

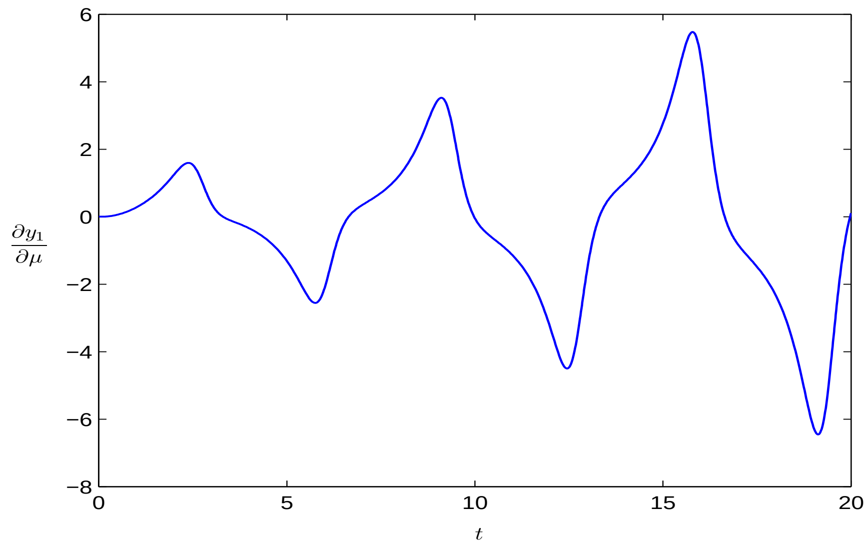
$$\Downarrow$$

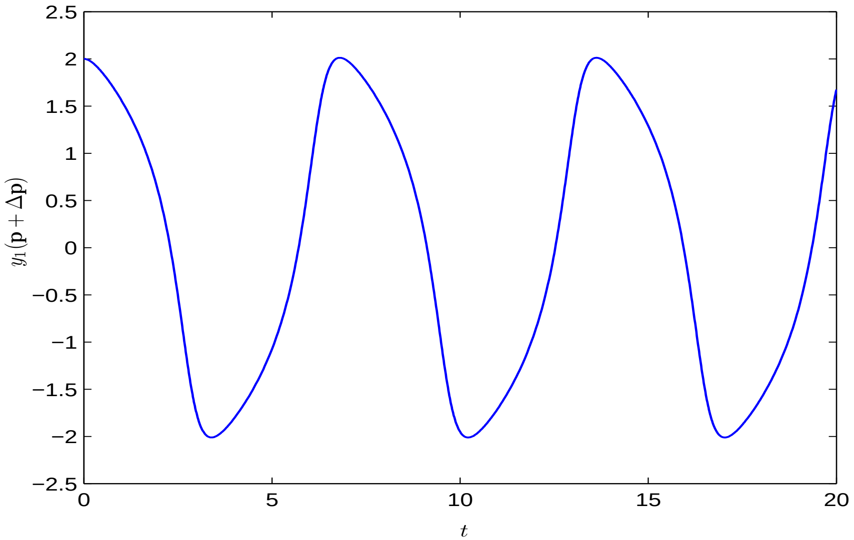
$$
\begin{aligned}
s'_{1_{(1)}}(t) &= {\color{red}s_{1_{(2)}}} \\
s'_{1_{(2)}}(t) &= (-2\mu y_1 y_2 - 1){\color{red}s_{1_{(1)}}} + \mu(1 - y_1^2){\color{red}s_{1_{(2)}}} + (1 - y_1^2)y_2
\end{aligned}
$$

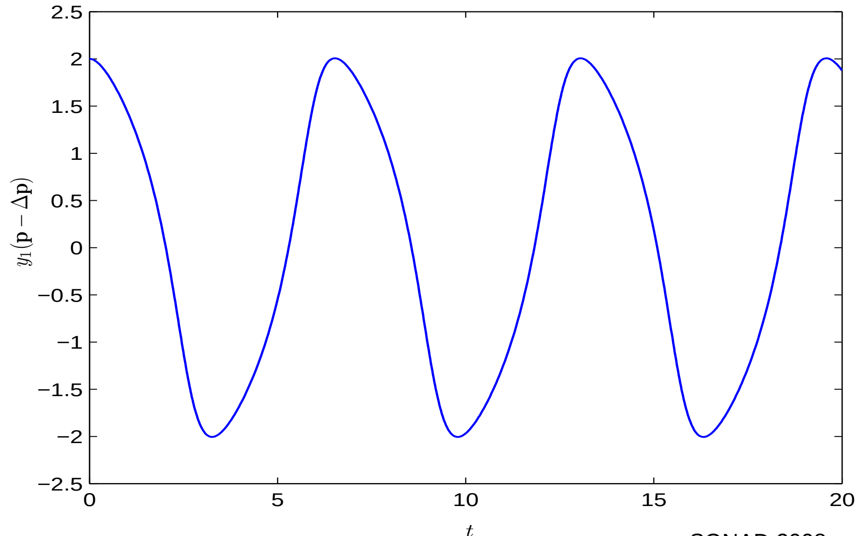
Numerical Sensitivity Analysis of IVPs - An Example

- The Van der Pol oscillator ($\Delta \mathbf{p} = 0.2$). The decrease of y_1 at $t = 20$ can be explained as second order sensitivities being dominant ($\frac{\partial y_1}{\partial \mu}(t = 20) \gtrapprox 0$, $\frac{\partial^2 y_1}{\partial \mu^2}(t = 20) < 0$).









DDEs and Sensitivity Analysis - Governing Equations

$$
\begin{aligned}
y'(t;\mathbf{p}) &= f(t, y(t;\mathbf{p}), y(\alpha(t,y;\mathbf{p});\mathbf{p}), y'(\alpha(t,y;\mathbf{p});\mathbf{p});\mathbf{p}) \\
y(t;\mathbf{p}) &= \phi(t;\mathbf{p}), \quad \text{for } t \le t_0(\mathbf{p})
\end{aligned}
$$

$$\Downarrow$$

Differentiation + Chain Rule + Clairaut's Theorem

$$\Downarrow$$

$$
\begin{aligned}
s_i'(t) = \frac{\partial f}{\partial y} s_i(t) \quad &+ \quad \frac{\partial f}{\partial y(\alpha_k)} \left(y'(\alpha_k) \left(\frac{\partial \alpha}{\partial y} s_i(t) + \frac{\partial \alpha}{\partial \mathbf{p}} \right) + s_i(\alpha) \right) \\
&+ \quad \frac{\partial f}{\partial y'(\alpha)} \left(y''(\alpha) \left(\frac{\partial \alpha}{\partial y} s_i(t) + \frac{\partial \alpha}{\partial \mathbf{p}} \right) + s_i'(\alpha) \right) \\
&+ \quad \frac{\partial f}{\partial \mathbf{p}}
\end{aligned}
$$

DDEs and Sensitivity Analysis - Proper Handling of Jumps

- Hybrid ODE systems [Tolsma & Barton]
  - Continuous transition at $t = \lambda$,

$$y(\lambda^+) = y(\lambda^-)$$

$$\Downarrow$$

$$\frac{\partial y}{\partial p_l}(\lambda^+) = \frac{\partial y}{\partial p_l}(\lambda^-) + \left(y'(\lambda^-) - y'(\lambda^+)\right) \frac{\partial \lambda}{\partial p_l}$$

  - Triggered by,

$$g(t, y, y'; \mathbf{p}) = 0$$

$$\Downarrow$$

$$\frac{\partial g}{\partial y'} \left(\frac{\partial}{\partial t} \left(\frac{\partial y}{\partial p_l} \right) + y'' \frac{\partial \lambda}{\partial p_l} \right) + \frac{\partial g}{\partial y} \left(\frac{\partial y}{\partial p_l} + y' \frac{\partial \lambda}{\partial p_l} \right) + \frac{\partial g}{\partial p_l} + \frac{\partial g}{\partial t} \frac{\partial \lambda}{\partial p_l} = 0$$

DDEs and Sensitivity Analysis - Proper Handling of Jumps

- DDEs
  - Discontinuity points of $y'(t;\mathbf{p})$,

$$\Lambda(\mathbf{p}) \equiv \{\lambda_1(\mathbf{p}), \lambda_2(\mathbf{p}), \ldots\}.$$

  - Identified by,

$$\alpha(\lambda_{r+1}(\mathbf{p}), y; \mathbf{p}) = \lambda_r(\mathbf{p}) \quad r = 1, 2, \ldots$$

  - Can be viewed as $\lambda_{r+1}(\mathbf{p})$ being a solution of,

$$\hat{g}(t, y; \mathbf{p}) = \alpha(t, y; \mathbf{p}) - \lambda_r(\mathbf{p}) = 0.$$

  - Using the result for hybrid ODEs,

$$\frac{\partial \lambda_{r+1}(\mathbf{p})}{\partial p_l} = -\frac{\frac{\partial \alpha}{\partial y}\frac{\partial y}{\partial p_l} + \frac{\partial \alpha}{\partial p_l} - \frac{\partial \lambda_r(\mathbf{p})}{\partial p_l}}{\frac{\partial \alpha}{\partial y} y' + \frac{\partial \alpha}{\partial t}} \quad \text{for } r \geq 1$$

$$\frac{\partial \lambda_1(\mathbf{p})}{\partial p_l} = \frac{\partial t_0(\mathbf{p})}{\partial p_l}$$

DDEs and Sensitivity Analysis - Proper Handling of Jumps

- Integration (first order sensitivities)
  1. Initialize ($\lambda_1 = t_0(\mathbf{p})$).
  2. $r \leftarrow 1$.
  3. Integrate the equations up to a C^1-discontinuity point (λ_{r+1}).
  4. Update the state variables (sensitivities) using

$$\frac{\partial y}{\partial p_l}(\lambda_{r+1}^{+}) = \frac{\partial y}{\partial p_l}(\lambda_{r+1}^{-}) + \left(y'(\lambda_{r+1}^{-}) - y'(\lambda_{r+1}^{+})\right) \frac{\partial \lambda_{r+1}(\mathbf{p})}{\partial p_l}$$

  5. $r \leftarrow r + 1$ and restart (3).

DDEs and Sensitivity Analysis - Examples

- The predator-prey model

$$
\begin{aligned}
y_1'(t) &= y_1(t)(1 - y_1(t-\tau) - \rho y_1'(t-\tau)) - \frac{y_2(t) y_1(t)^2}{y_1(t)^2 + 1} \\
y_2'(t) &= y_2(t) \left(\frac{y_1(t)^2}{y_1(t)^2 + 1} - \alpha \right)
\end{aligned}
$$

where $\alpha = 1/10$, $\rho = 29/10$ and $\tau = 21/50$, for t in $[0, 30]$. The history functions are

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\phi_1(t) &= \frac{33}{100} - \frac{1}{10} t \\
\phi_2(t) &= \frac{111}{50} + \frac{1}{10} t
\end{aligned}
$$

for $t \leq 0$.

Parameters are

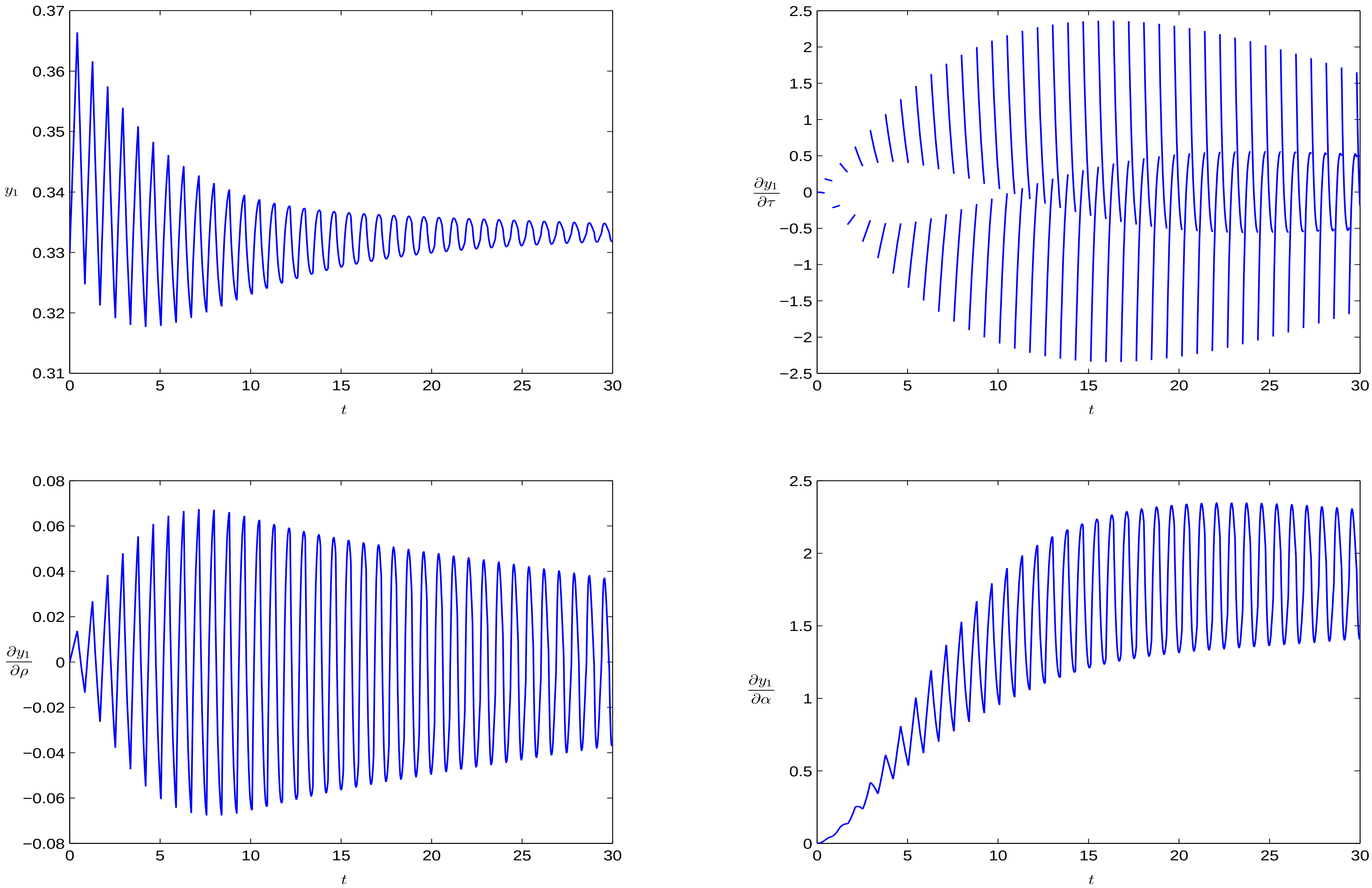
$$
\mathbf{p} = [\tau,\ \rho,\ \alpha,\ \mathrm{a},\ \mathrm{b},\ \mathrm{c},\ \mathrm{d}]
$$

where

$$
\begin{aligned}
\phi_1(t) &= \mathrm{a} + \mathrm{b}\, t \\
\phi_2(t) &= \mathrm{c} + \mathrm{d}\, t
\end{aligned}
$$

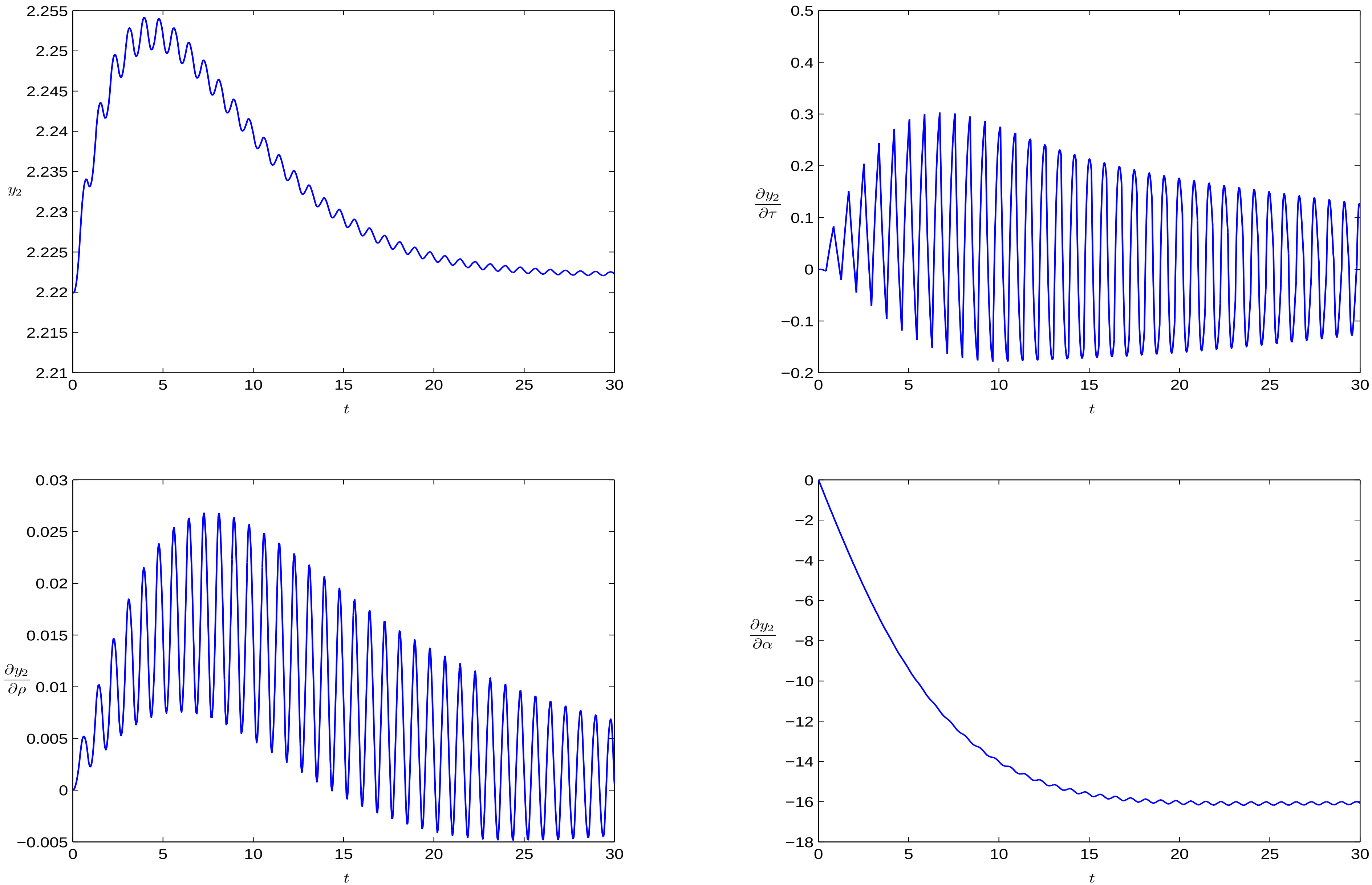
DDEs and Sensitivity Analysis - Examples

- The predator-prey model (structure-related parameters, y_1)



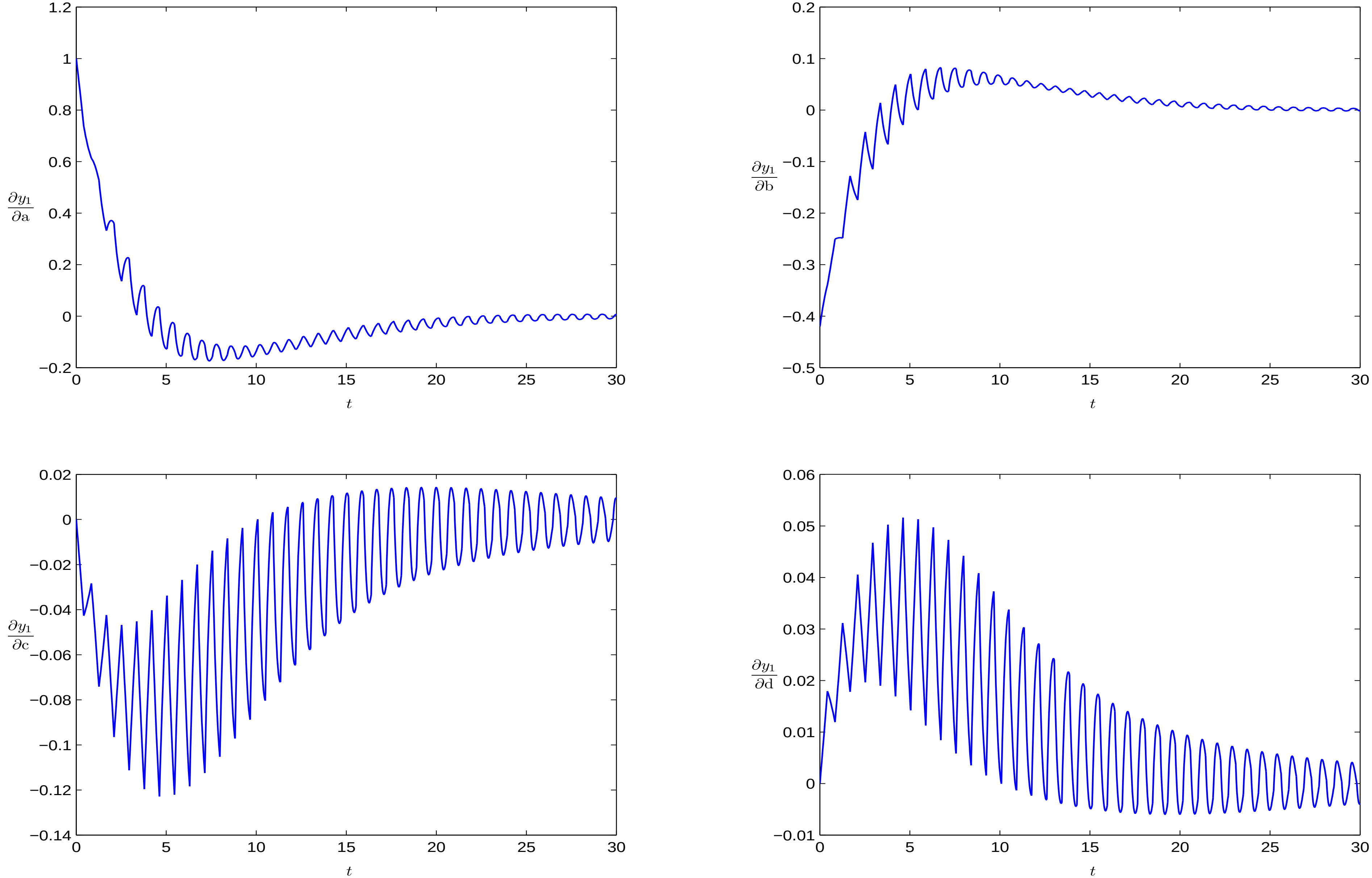
DDEs and Sensitivity Analysis - Examples

- The predator-prey model (structure-related parameters, y_2)



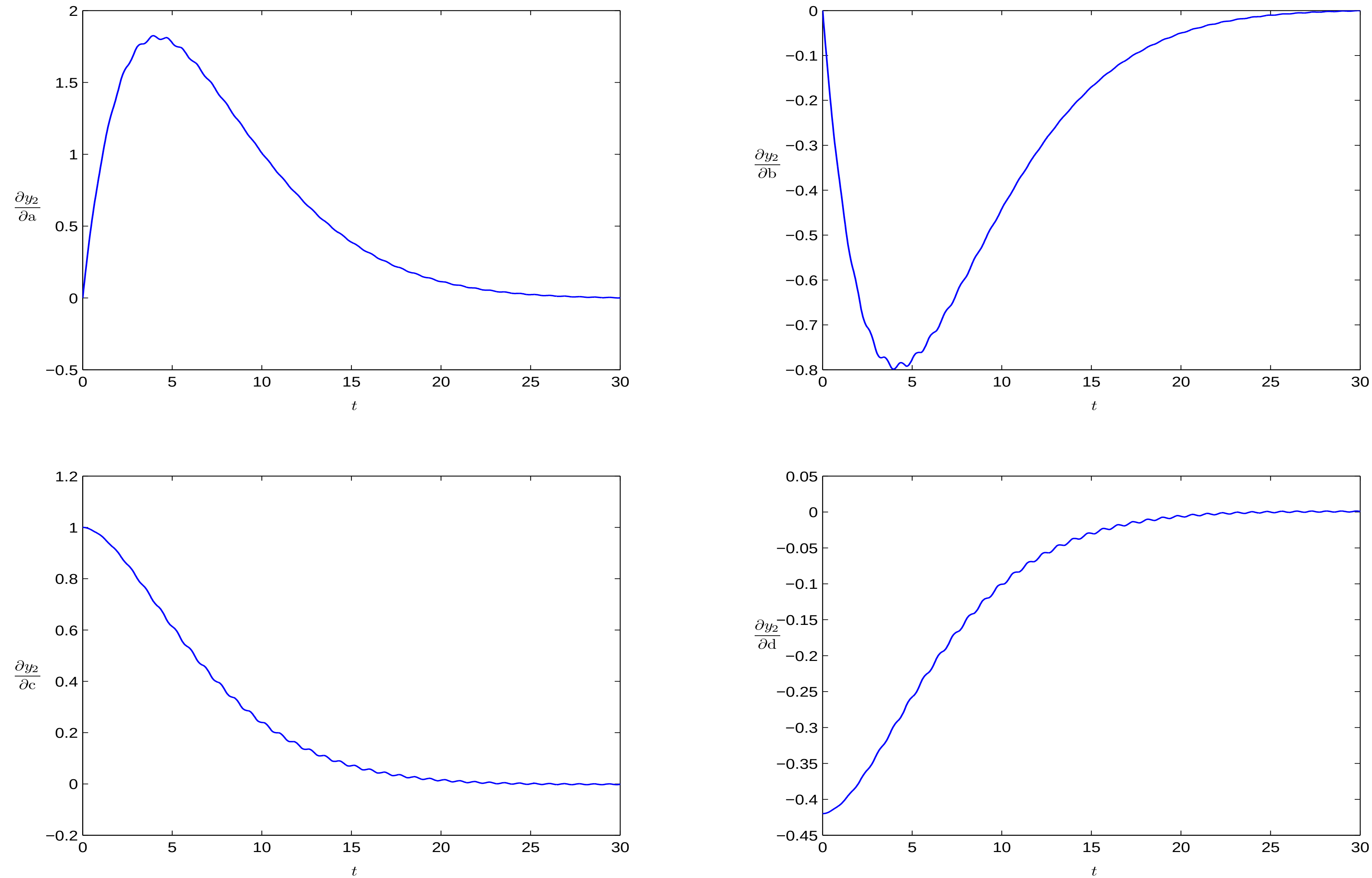
DDEs and Sensitivity Analysis - Examples

- The predator-prey model (history-related parameters, y_1)



DDEs and Sensitivity Analysis - Examples

- The predator-prey model (history-related parameters, y_2)



Modeling and Parameter Estimation - Definitions

- Parameter Estimation Problem
  - A System of Parameterized IVP

$$\begin{aligned} y'(t;\mathbf{p}) &= f(t, y(t;\mathbf{p});\mathbf{p}) \\ y(t_0) &= y_0(\mathbf{p}) \end{aligned}$$

or DDE

$$\begin{aligned} y'(t;\mathbf{p}) &= f(t, y(t;\mathbf{p}), y(t-\sigma(t;\mathbf{p}));\mathbf{p}) \ \text{ for } \ t_0(\mathbf{p}) \le t \\ y(t;\mathbf{p}) &= \phi(t;\mathbf{p}), \ \text{ for } \ t \le t_0(\mathbf{p}) \end{aligned}$$

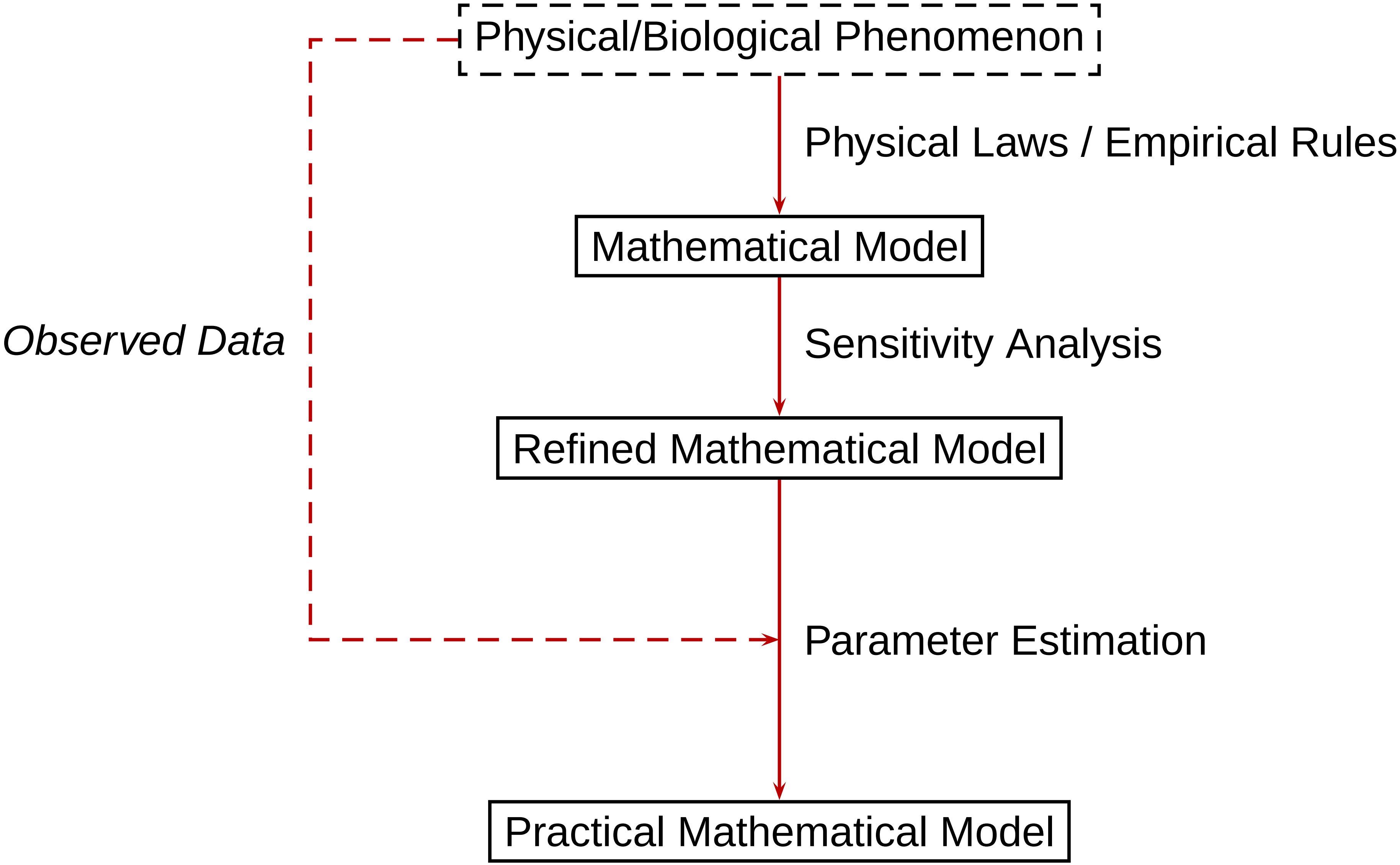
  - A Set of Data (Observations/Measurements)

$$\{Y(\gamma_i) \approx y(\gamma_i;\mathbf{p}^\star)\}$$

  - Estimate $\mathbf{p}^\star$ by minimizing an objective function.
e.g.

$$W(\mathbf{p}) = \sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]^2 .$$

Modeling and Parameter Estimation - Importance



Modeling and Parameter Estimation - Optimizers

- Algorithms for Nonlinear Least-Squares
  - Unconstrained

$$\min_{\mathbf{p}} W(\mathbf{p}) = \sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]^2 .$$

$$\downarrow$$

Levenberg-Marquardt

Variations of Sequential Quadratic Programming (SQP)

  - Constrained

$$\begin{aligned} \min_{\mathbf{p}} W(\mathbf{p}) = \sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]^2 , \\ c_j(\mathbf{p}) = 0, \quad j \in \mathcal{E}, \\ c_j(\mathbf{p}) \geq 0, \quad j \in \mathcal{I}. \end{aligned}$$

$$\downarrow$$

Sequential Quadratic Programming (SQP)

- The *smoothness* of functions involved in the problem, the objective function and constraints, is a *necessary* assumption.

Numerical Parameter Estimation of IVPs

Steps :

1. Choose an initial guess for the parameters
2. Solve model equations
3. Check optimality conditions, (if satisfied $\Rightarrow$ stop).
4. Choose a better value for the parameters and continue with (2)

If the optimization method needs to compute the gradient or the Hessian of the objective function,

$$\left(\frac{\partial W(\mathbf{p})}{\partial p_l}\right) = -2\sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)$$

$$\left(\frac{\partial^2 W(\mathbf{p})}{\partial p_l \partial p_m}\right) = 2\sum_i \left[\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_m}\right) - \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial^2 y(\gamma_i;\mathbf{p})}{\partial p_l \partial p_m}\right)\right]$$

the sensitivity equations are usually used to provide the required values. An alternative approach is to use a divided-difference approximation.

DDEs and Parameter Estimation

[Paul , 1997] :

Assume that jumps in the derivative of $y(t;\mathbf{p})$ with respect to t occur at the points

$$\Lambda(\mathbf{p}) \equiv \{\lambda_1(\mathbf{p}), \lambda_2(\mathbf{p}), \ldots\}.$$

Such discontinuities, when arising from the initial point $t_0(\mathbf{p})$ (and the initial function $\phi(t;\mathbf{p})$), may propagate into $W(\mathbf{p})$ via the solution values $\{y(\gamma_i;\mathbf{p})\}$.

The first and second order partial derivatives of the objective function are

$$\left(\frac{\partial W(\mathbf{p})}{\partial p_l}\right)_{\pm} = -2\sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)_{\pm}$$

$$\left(\frac{\partial^2 W(\mathbf{p})}{\partial p_l \partial p_m}\right)_{\pm\pm} = 2\sum_i \left[\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)_{\pm}\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_m}\right)_{\pm} - \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial^2 y(\gamma_i;\mathbf{p})}{\partial p_l \partial p_m}\right)_{\pm\pm}\right]$$

DDEs and Parameter Estimation

- Non-smooth optimization
  - Consider the continuous function

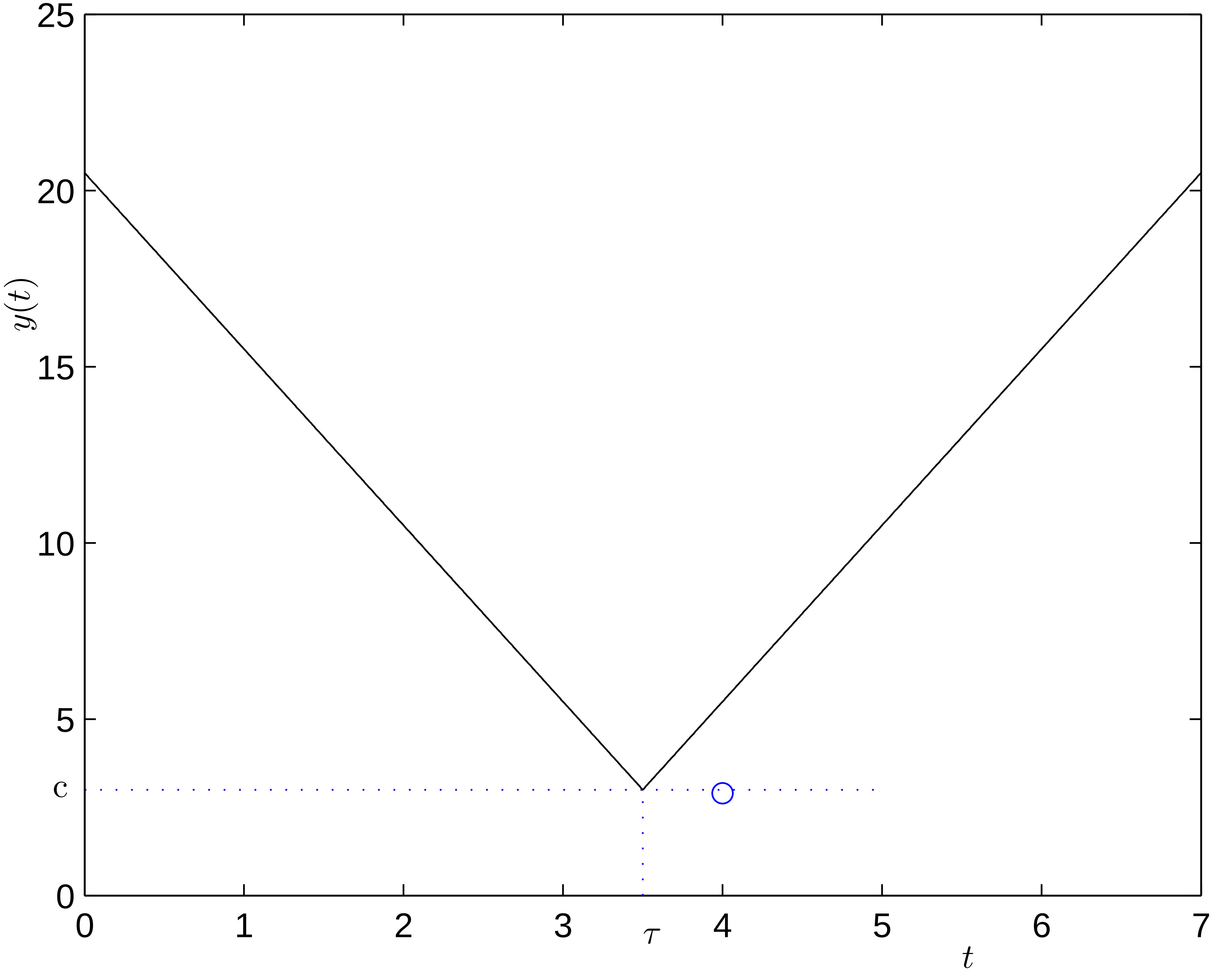
$$y(t) = \begin{cases} -5(t-\tau) + \mathrm{c}, & \text{if } t < \tau \\ 5(t-\tau) + \mathrm{c}, & \text{if } t \geq \tau \end{cases}$$

  - with discontinuous derivative

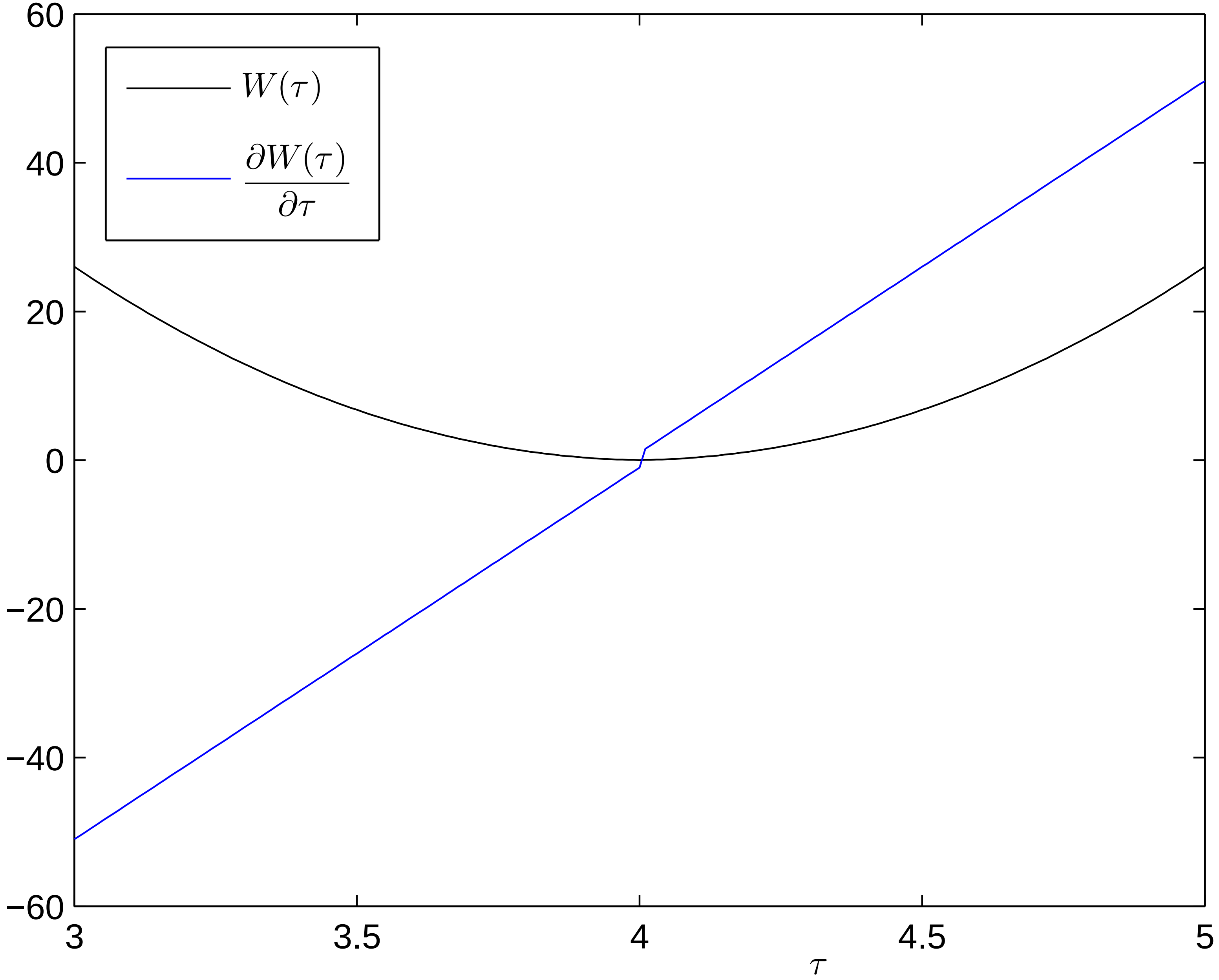
$$y'(t) = \begin{cases} -5, & \text{if } t < \tau \\ 5, & \text{if } t \geq \tau \end{cases}$$

  - and observed value of y at the discontinuity point $\tau^\star = 4$.

DDEs and Parameter Estimation



DDEs and Parameter Estimation



DDEs and Parameter Estimation

- Try to find $\tau^\star$ using MATLAB's unconstrained minimization routine *fminunc*

$$\Downarrow$$

$$31 \text{ iterations .}$$

- Try to use MATLAB's constrained minimization routine *fmincon* with the added constraint

$$\tau \leq 4$$

$$\Downarrow$$

$$2 \text{ iterations .}$$

- Try to use MATLAB's constrained minimization routine *fmincon* with the added constraint

$$\tau \geq 4$$

$$\Downarrow$$

$$2 \text{ iterations .}$$

DDEs and Parameter Estimation - Safe Minimization

Appearance of Non-smoothness

- Partial derivatives(gradient) of the objective function

$$\left(\frac{\partial W(\mathbf{p})}{\partial p_l}\right)_{\pm} = -2\sum_i \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)_{\pm}$$

$$\left(\frac{\partial^2 W(\mathbf{p})}{\partial p_l \partial p_m}\right)_{\pm\pm} = 2\sum_i \left[\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_l}\right)_{\pm}\left(\frac{\partial y(\gamma_i;\mathbf{p})}{\partial p_m}\right)_{\pm} - \left[Y(\gamma_i) - y(\gamma_i;\mathbf{p})\right]\left(\frac{\partial^2 y(\gamma_i;\mathbf{p})}{\partial p_l \partial p_m}\right)_{\pm\pm}\right]$$

- Recall the jump equation for sensitivities

$$\frac{\partial y}{\partial p_l}(\lambda_{r+1}^{+}) = \frac{\partial y}{\partial p_l}(\lambda_{r+1}^{-}) + \left(y'(\lambda_{r+1}^{-}) - y'(\lambda_{r+1}^{+})\right)\frac{\partial \lambda_{r+1}(\mathbf{p})}{\partial p_l}$$

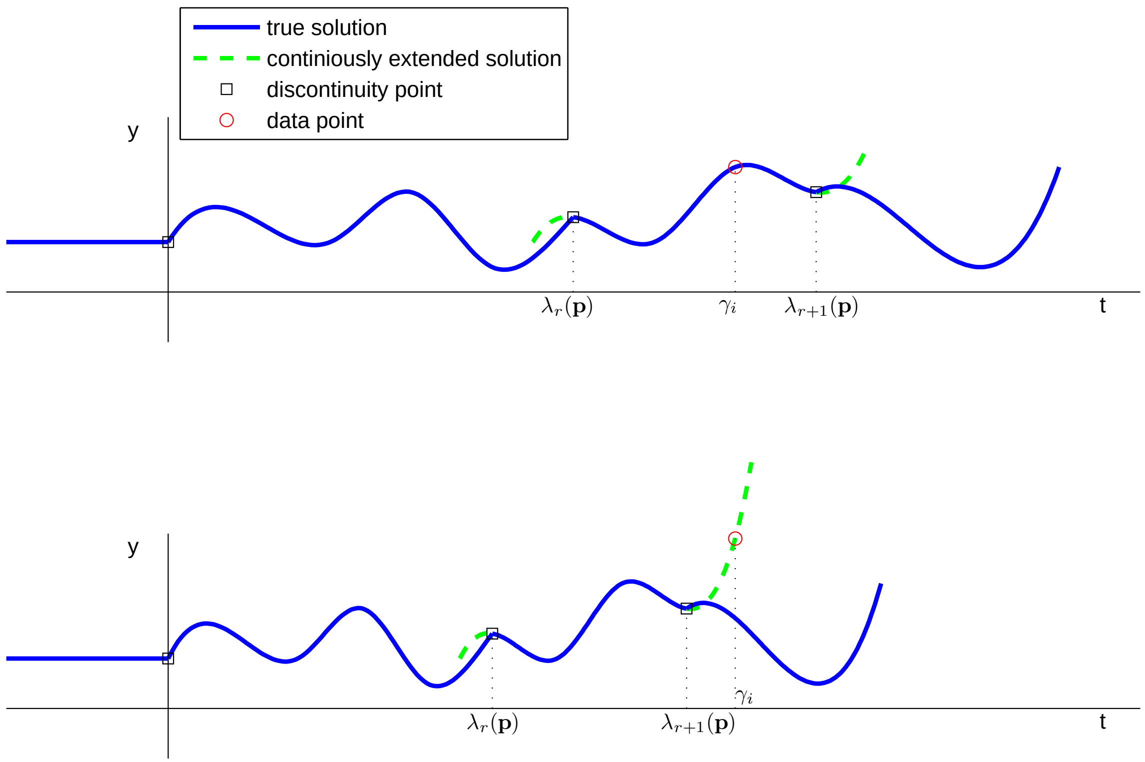
$$\Downarrow$$

- The General Rule : A jump occurs in $W(\mathbf{p})$ when

$$\boxed{\text{a discontinuity point } \lambda_{r+1}(\mathbf{p}) \text{ passes a data point } \gamma_i}$$

DDEs and Parameter Estimation - Safe Minimization

Avoiding The Non-smoothness



Force the ordering by adding $\lambda_r(\mathbf{p}) \leq \gamma_i \leq \lambda_{r+1}(\mathbf{p})$ to the set of constraints.

The partial derivatives (gradient) of the new constraints , $\frac{\partial \lambda_{r+1}(\mathbf{p})}{\partial \mathbf{p}}$, can be computed recursively.

DDEs and Parameter Estimation - A Test Case

- Estimating τ for the predator-prey model

$$\begin{aligned} y_1'(t) &= y_1(t)(1 - y_1(t-\tau) - \rho y_1'(t-\tau)) - \frac{y_2(t)y_1(t)^2}{y_1(t)^2+1} \\ y_2'(t) &= y_2(t)\left(\frac{y_1(t)^2}{y_1(t)^2+1} - \alpha\right) \end{aligned}$$

- Start with up to 10% random perturbation in original τ,
  and up to 3% randomly perturbed $y(t;\tau)$ as Data (Y).
  For γ's we choose 10 random points, one of which is a discontinuity point.
- Run the parameter estimator 3 times.
- Results

Estimator Choice	FCN	OBJ
Very Simple	72,2697	0.000142917
Using Sensitivities	26,942	0.000142917
Adding Constraints	9,916	0.000142917