

PARAMETRIC SENSITIVITY ANALYSIS OF NONLINEAR MULTIPARAMETER REGRESSION MODEL SYSTEMS

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Motivation

Parametric sensitivities in nonlinear regression describe the impact of perturbations in model parameter estimates on predicted responses. Poor precision in parameter estimates leads to poor precision in predicted responses when sensitivities are large.

Uses

- identification of influential parameters
- guide further experimentation to reduce uncertainties

Sensitivities are in the context of -
 – specified model formulation: *structure & parameterization*
 – specified dataset: *run conditions & designed experiments*

Multiparameter Regression Models

Uniresponse Model

- N runs

$$y_j = \eta_j(\Theta) + \varepsilon_j = f(\mathbf{x}_j, \Theta) + \varepsilon_j, j=1, \dots, N$$

$$\mathbf{y} = \boldsymbol{\eta}(\Theta) + \boldsymbol{\varepsilon}$$

Multiresponse Model

- N runs, M responses

$$\mathbf{y}_{nm} = f_m(\mathbf{x}_n, \Theta) + \varepsilon_{nm}, n=1, \dots, N; m=1, \dots, M$$

$$\mathbf{Y} = \mathbf{H}(\Theta) + \mathbf{Z}$$

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Profile-Based Sensitivity Coefficient (PSC)

- Motivated by profiling algorithm of Bates and Watts (1988) for producing profile plots

$$\tau(\theta_i) = \text{sign}(\theta_i - \hat{\theta}_i) \sqrt{F(\theta_i)}$$

$$F(\theta_i) = \frac{S(\theta_i, \tilde{\Theta}_{-i}(\theta_i)) - S(\hat{\Theta})}{S(\hat{\Theta}) / (N - p)}$$

- Profile traces - plots of conditional estimate of one parameter vs. another parameter, with remaining parameters held at their conditional estimates
- Profile t-plots of $\tau(\theta_i)$ versus θ_i . Show the extent of the parameter nonlinearities in the model.
- indicates both nonlinearity and extent of correlation between parameter estimates.

Profile-Based Sensitivity Coefficient

- prediction parameter transformation

- re-assign parameter to be prediction at a specific point
- profile trace of this parameter provides a graphical indication of sensitivity of prediction to perturbations in other parameters
- motivates definition of profile-based sensitivity as:

- total derivative of the predicted response at a point with respect to a given parameter, with other parameter estimates held at their conditional least squares values

Profile-Based Sensitivity Coefficient – Uniresponse

Definition - Uniresponse Case
(Sulieman, 1998, Sulieman et al., 2001)

$$\begin{aligned} PSC_i(x_0) &= \frac{D\eta_0(\theta_i, \Theta_{-i}(\theta_i))}{D\theta_i} = \left. \frac{\partial \eta_0}{\partial \theta_i} + \frac{\partial \eta_0}{\partial \Theta_{-i}} \right|_{\tilde{\Theta}_{-i}} \frac{\partial \tilde{\Theta}_{-i}}{\partial \theta_i} \\ &= \left. \frac{\partial \eta_0}{\partial \theta_i} - \frac{\partial \eta_0}{\partial \Theta_{-i}} \left(\frac{\partial^2 S}{\partial \Theta_{-i} \partial \Theta'_{-i}} \right)^{-1} \frac{\partial^2 S}{\partial \theta_i \partial \Theta'_{-i}} \right|_{\tilde{\Theta}_{-i}(\theta_i)} \\ &= MSC(x_0) + \text{correction term} \end{aligned}$$

Marginal sensitivity coefficient: $MSC_i(x_0) = \frac{\partial \eta_0}{\partial \theta_i}$
Correction term: accounts for correlation between parameter estimates & nonlinearity

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Profile-Based Sensitivity Coefficient - Uniresponse

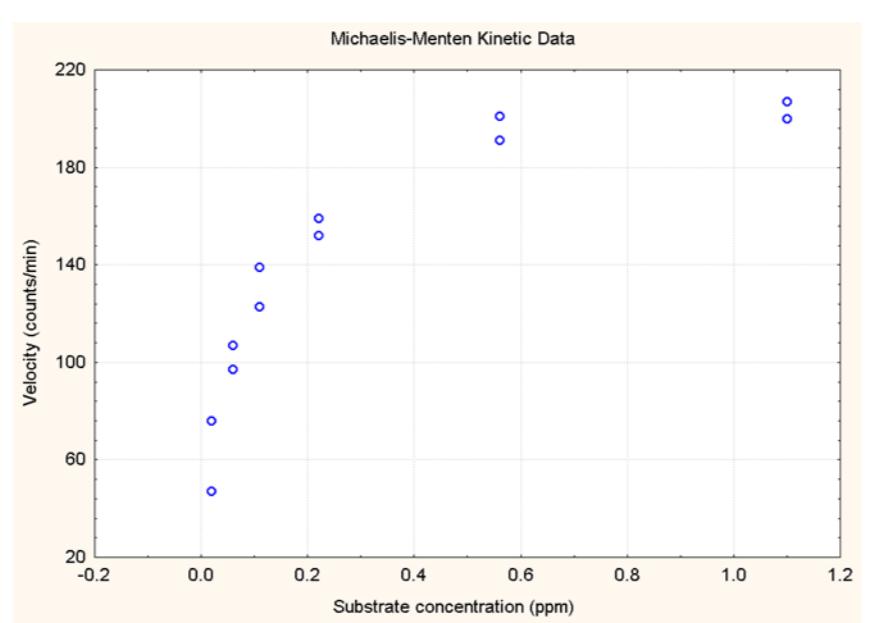
Computational issues

- scaling
 - work with studentized parameters and predicted responses to remove scale dependence
 - centering by least squares estimate
 - scaling by standard error
 - dimensionless sensitivity coefficients
- derivative values
 - algebraic models - obtain directly
 - differential equation models - via first- and second-order sensitivity equations
 - velocity and acceleration arrays are involved in PSC

Example - Uniresponse PSC

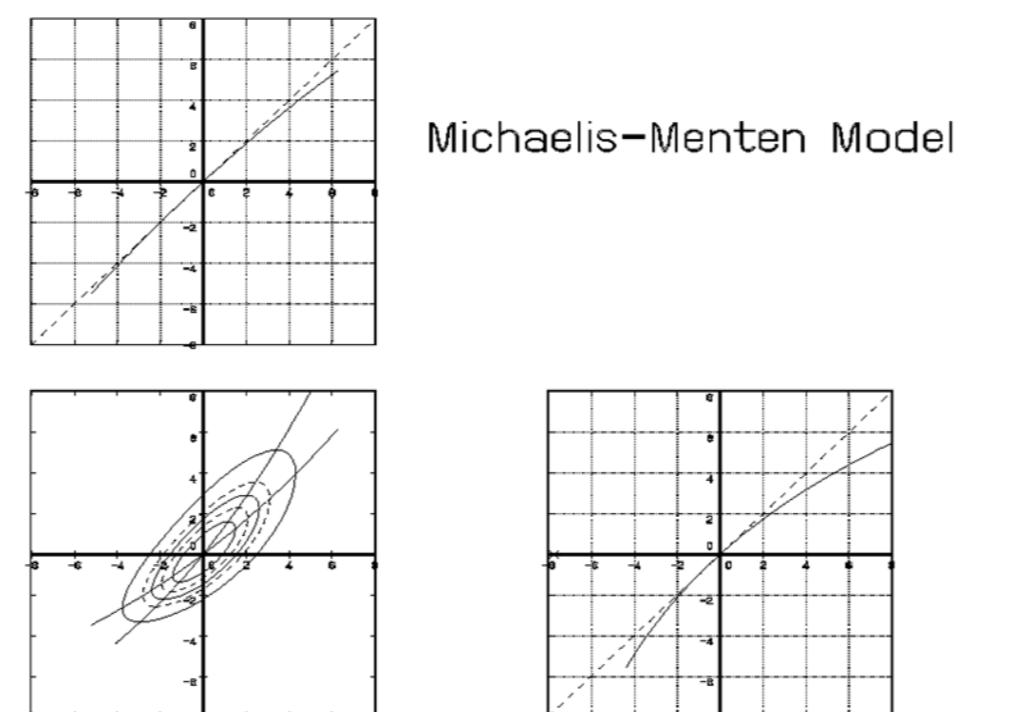
Michaelis-Menten model

- dataset from Bates and Watts (1988)
- model equation $f(x, \theta) = \frac{\theta_1 x}{\theta_2 + x}$



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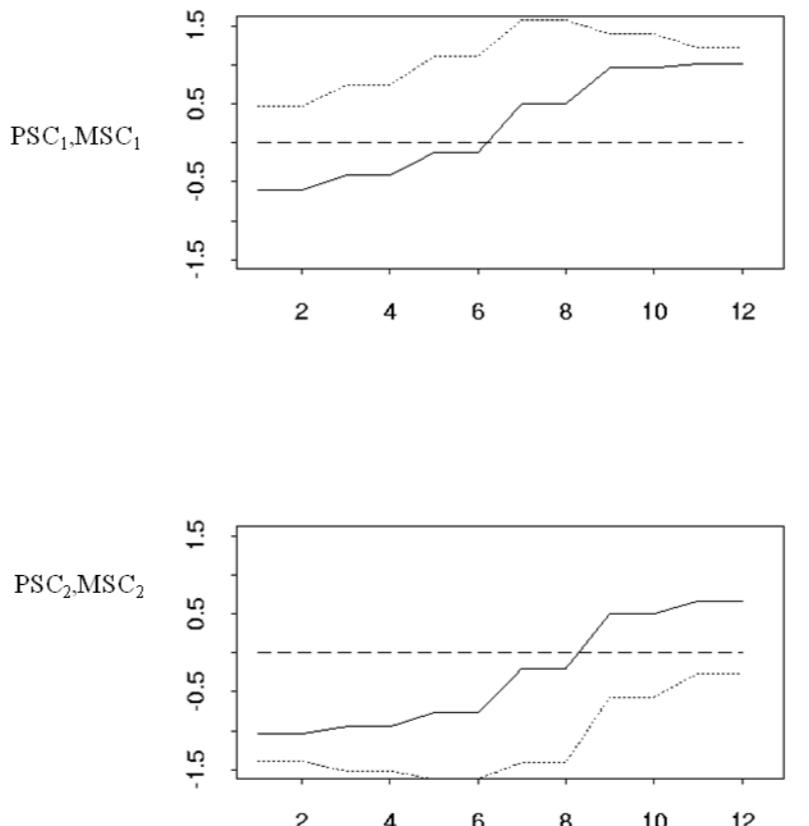
Profile traces



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Example - Uniresponse PSC

Graphical summaries of PSC values



Solid line - PSC
Dashed line - MSC

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Example - Uniresponse PSC

Interpretation

- for θ_1
 - PSC, MSC similar at high substrate
 - reduced correlation between parameter estimates
 - θ_1 defines asymptote at high concentration
 - significant difference between MSC, PSC at mid-range
 - MSC indicates significant sensitivity, while PSC indicates negligible sensitivity
- for θ_2
 - MSC, PSC similar at low substrate
 - reduced correlation between parameter estimates
 - θ_2 defines behaviour at low substrate concentrations
 - PSC indicates more significant sensitivity at higher substrate - through parameter correlation

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Multiresponse PSC

In this case, the parameter estimates are determined to minimize the Box-Draper determinant criterion:

$$d(\Theta) = |\mathbf{Z}'\mathbf{Z}|$$

The vector of predicted responses at a nominal run condition is denoted as:

$$\mathbf{H}_0(\Theta) = [f_1(\mathbf{x}_0, \Theta) \dots f_M(\mathbf{x}_0, \Theta)]$$

The PSC is again defined as a total derivative, yielding a **vector** of PSC values in this instance:

$$\begin{aligned} PSC_i(\mathbf{x}_0) &= \frac{D\mathbf{H}'_0(\theta_i, \Theta_{-i}(\theta_i))}{D\theta_i} = \left. \frac{\partial \mathbf{H}'_0}{\partial \theta_i} + \frac{\partial \mathbf{H}'_0}{\partial \Theta_{-i}} \frac{\partial \Theta_{-i}}{\partial \theta_i} \right|_{\tilde{\Theta}_{-i}} \\ &= MSC_i(\mathbf{x}_0) + \text{correction vector} \end{aligned}$$

Multiresponse PSC

Computational Issues

- scaling
 - use similar studentization approach - centering by Box-Draper estimates and scaling by standard errors
- derivatives
 - Hessian of determinant computed using identity due to Federov (1972): $\frac{\partial^2 d}{\partial \theta_r} = |\mathbf{Z}'\mathbf{Z}| \mathbf{Z} (\mathbf{Z}'\mathbf{Z})^{-1} \frac{\partial (\mathbf{Z}'\mathbf{Z})}{\partial \theta_r}$
 - differential equation models - 1st and 2nd-order derivatives computed from sensitivity equations
- conditioning
 - dependencies can occur in response data, leading to singular residual matrix and spurious optima

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Multiresponse PSC Example

Dow Chemical regression benchmark

- isothermal batch reactor
- dataset consists of concentration profiles over time for batches run at 3 different temperatures
- data for three species used - three response variables, y_1, y_2, y_3
- model structure included eight unknown parameters ($k_{10}, k_{20}, k_{12}, k_{10}^B, k_{20}^B, \beta_1, \beta_2$)
- measurement times differ for each profile, and are sampled at non-uniform intervals
- considered by Biegler et al. (1986), Biegler et al. (1991), Guay and McLean (1995)

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Example - Multiresponse PSC

Dow Chemical regression benchmark example - model

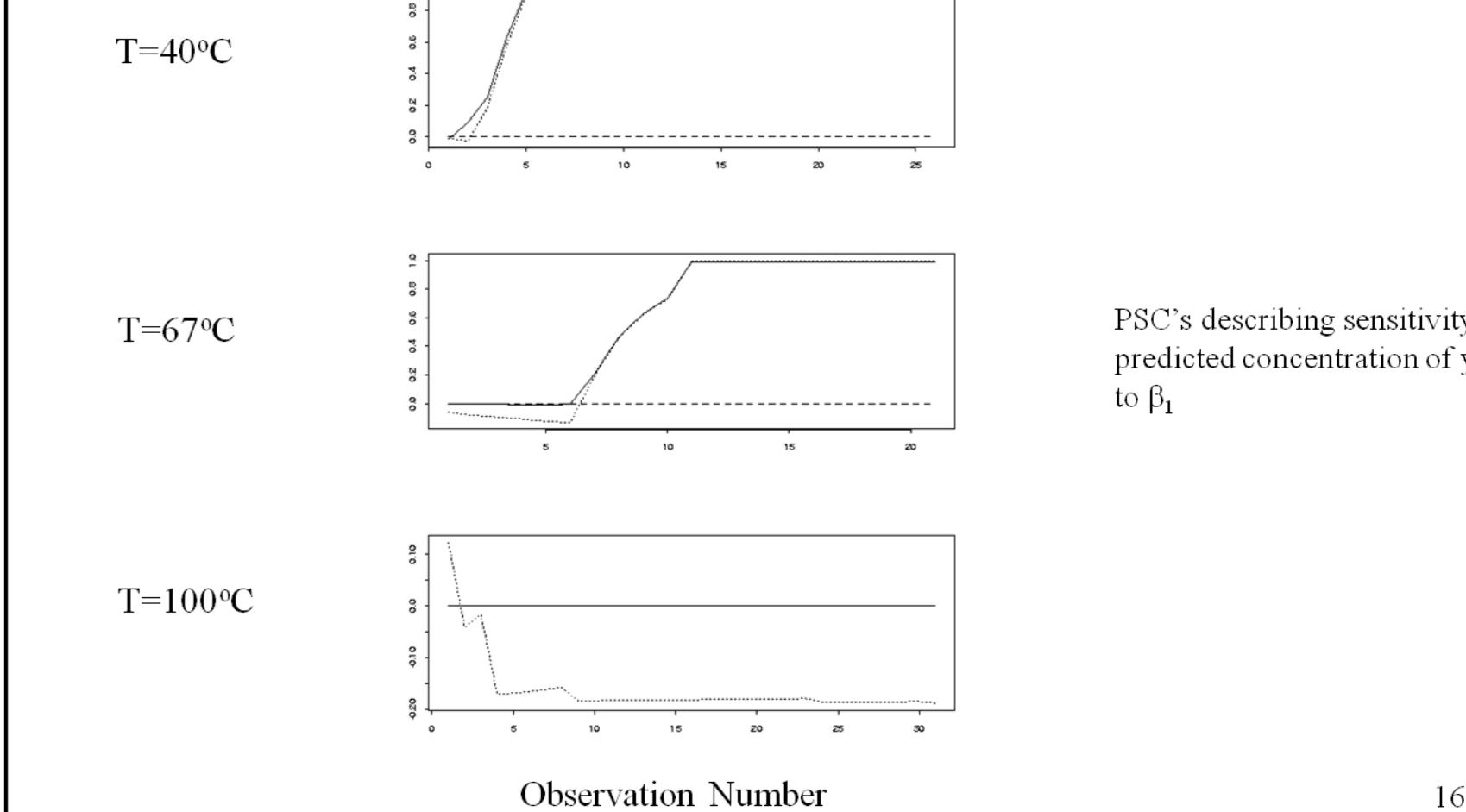
$$\begin{aligned} \frac{dy_1}{dt} &= -k_2 y_1 y_2 A \\ \frac{dy_2}{dt} &= -k_1 y_2 (x_2 + 2x_3 - x_4 - 2y_1 + y_2 - y_3) - k_2 y_1 y_2 A + k_1 \beta_1 (-x_3 + x_4 + y_1 - y_2) A \\ \frac{dy_3}{dt} &= k_1 (x_3 - y_1 - y_3) (x_2 + 2x_3 - x_4 - 2y_1 + y_2 - y_3) + k_2 y_1 y_2 A - \frac{1}{2} k_1 \beta_2 y_3 A \end{aligned}$$

where

$$\begin{aligned} k_i &= k_{i0} \exp\left(\frac{E_i}{R} \left(\frac{1}{T_i} - \frac{1}{T_0}\right)\right), i=-1,1,2 \\ A &= \frac{-2x_3 + x_4 + 2y_1 - y_2 + y_3}{y_1 + \beta(-x_3 + x_4 + y_1 - y_2) + \beta_2 y_3} \\ \beta_1 &= \frac{K_1}{K_2}, \beta_2 = \frac{K_3}{K_2} \end{aligned}$$

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Multiresponse PSC Example

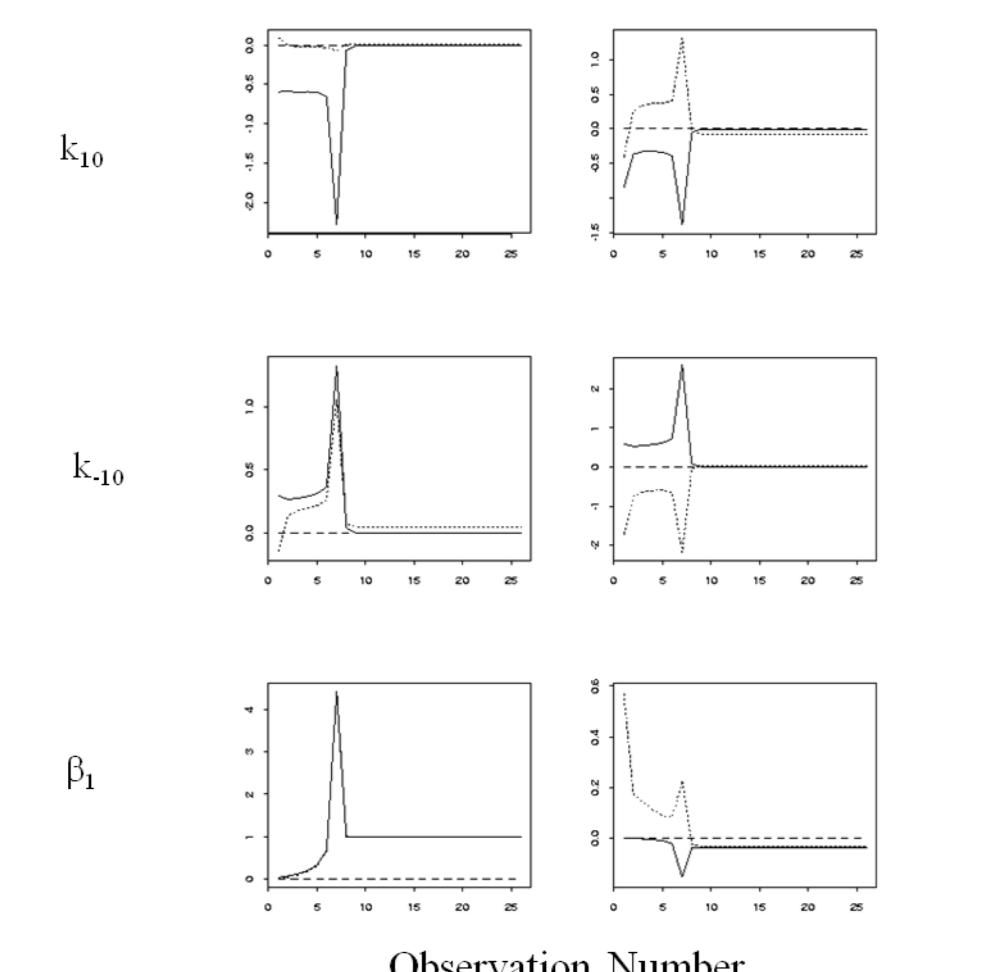


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Multiresponse PSC Example

PSC's describing sensitivity of predicted concentration of y_2 to selected parameters at 40°C



Example - Multiresponse PSC

- interpretation - y_3 to β_1 at three temps
 - close agreement of msc, psc at low, moderate T, but changes dramatically at high T - marginal sensitivities negligible at high T, but psc indicates significant sensitivities - consequence of parameter correlation and model behaviour over three temperatures
- y_2 to params at 40 C
 - general pattern - significant sensitivities at low times (early in batch) - where bulk of concentration changes occur - not surprising - msc's indicate sensitivities where psc's are negligible - suggestion that correlation counteracts marginal sensitivities ... - discrepancies over early part of run - where major changes are occurring

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Summary and Conclusions

- Reliability of parametric sensitivity results greatly depends on:
 - perturbation scheme used to vary parameter values
 - underlying assumption about model structure
- Profile-based sensitivity coefficients (PSC's) adjust the marginal sensitivity behavior to account for:
 - correlation structure among parameter estimates
 - nonlinearity in model parameters
- PSC's are defined as total derivative of predicted response with respect to parameter of interest
 - for uni-response, via least squares criterion
 - for multi-response, via determinant criterion
- PSC's provide more accurate reflection of impact of parameter perturbation when all other parameters are adjusted to provide best fit
- quantitative measure that can be combined with graphical summaries - profile traces

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References

- Sulieman, H., McLellan, P.J., and Bacon, D. W., (2004) "A Profile-Based Approach to Parametric Sensitivity in Multiresponse Regression Models", *Computational Statistics and Data Analysis*, vol. 45, No. 4, pp. 721-740.
- Sulieman, H., McLellan, P.J., and Bacon, D. W. (2001), "A Profile-Based Approach to Parametric Sensitivity Analysis in Nonlinear Regression Models", *Technometrics*, vol. 43, No. 4, pp. 425-433.

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