Interval analysis
for guaranteed Parameter Estimation

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joint work with L. Jaulin and E. Walter

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1 Interval analysis

Provides efficient techniques to

- perform guaranteed deterministic global optimization,
- evaluate all solutions of a set of nonlinear equations
- compute inner and outer approximation of the set of vectors consistent with a set of inequalities
- ...

Has lead to numerous applications

- Bounded-error parameter and state estimation of nonlinear systems
- Robust bounded-error parameter and state estimation
- Parameter estimation by global optimization
- Structural identifiability study
- Distributed estimation
- ...

1.1 Interval arithmetic primer

Introduced by Sunaga in Japan and by Moore in the USA.

Limited impact until beginning of the 90s

$\Longrightarrow$ various reasons, among which implementation issues

Many books, code libraries, lists

`http://www.cs.utep.edu/interval-comp/main.html`

1.1.1 Interval of real numbers

Closed and *bounded* subset of $\mathbb{R}$

$$[x] = [\underline{x}, \overline{x}] = \{x \in \mathbb{R} | \underline{x} \leq x \leq \overline{x}\}\,.$$

It is a set $\Longrightarrow$ notions such as

$$=, \in, \subset, \cap$$

are well defined.

When considering $\cup$

$$[x] \cup [y] = \left[\min(\underline{x}, \underline{y}), \max(\overline{x}, \overline{y})\right]\,.$$

Other characteristics of an interval

Width

$$w\left([x]\right) = \overline{x} - \underline{x},$$

Midpoint

$$m\left([x]\right) = \frac{\underline{x} + \overline{x}}{2}.$$

1.1.2 Basic operations

May be extended to intervals

$$\circ \in \{+, -, \times, /\}, \ [x] \circ [y] = \{x \circ y | x \in [x] \text{ et } y \in [y]\}.$$

More specifically

$$\begin{cases} [x] + [y] = \left[\underline{x} + \underline{y}, \overline{x} + \overline{y}\right], \\ [x] - [y] = \left[\underline{x} - \overline{y}, \overline{x} - \underline{y}\right], \\ [x] \times [y] = \left[\min\left(\underline{x}.\underline{y}, \overline{x}.\underline{y}, \underline{x}.\overline{y}, \overline{x}.\overline{y}\right), \max\left(\underline{x}.\underline{y}, \overline{x}.\underline{y}, \underline{x}.\overline{y}, \overline{x}.\overline{y}\right)\right], \\ [x] / [y] = [x] \times \left[1/\overline{y}, 1/\underline{y}\right], \text{si } 0 \notin [y] \text{ et ind fini sinon.} \end{cases}$$

1.1.3 Inclusion function

Range of a function over an interval

$$f([x]) = \{f(x) \,|x \in [x]\}$$

$\Longrightarrow$ difficult to obtain in general

$\Longrightarrow$ sometimes even not an interval

Inclusion function $[f](.)$ of $f(.)$ satisfies

$$\forall [x] \subset \mathbb{R},\ f([x]) \subset [f]([x]).$$

Inclusion function is minimal if $\subset$ may be replaced by $=$.

Convergent inclusion function

$$\text{if } w([x]) \to 0, \text{ then } w([f]([x])) \to 0.$$

Inclusion function easy to build for monotone functions

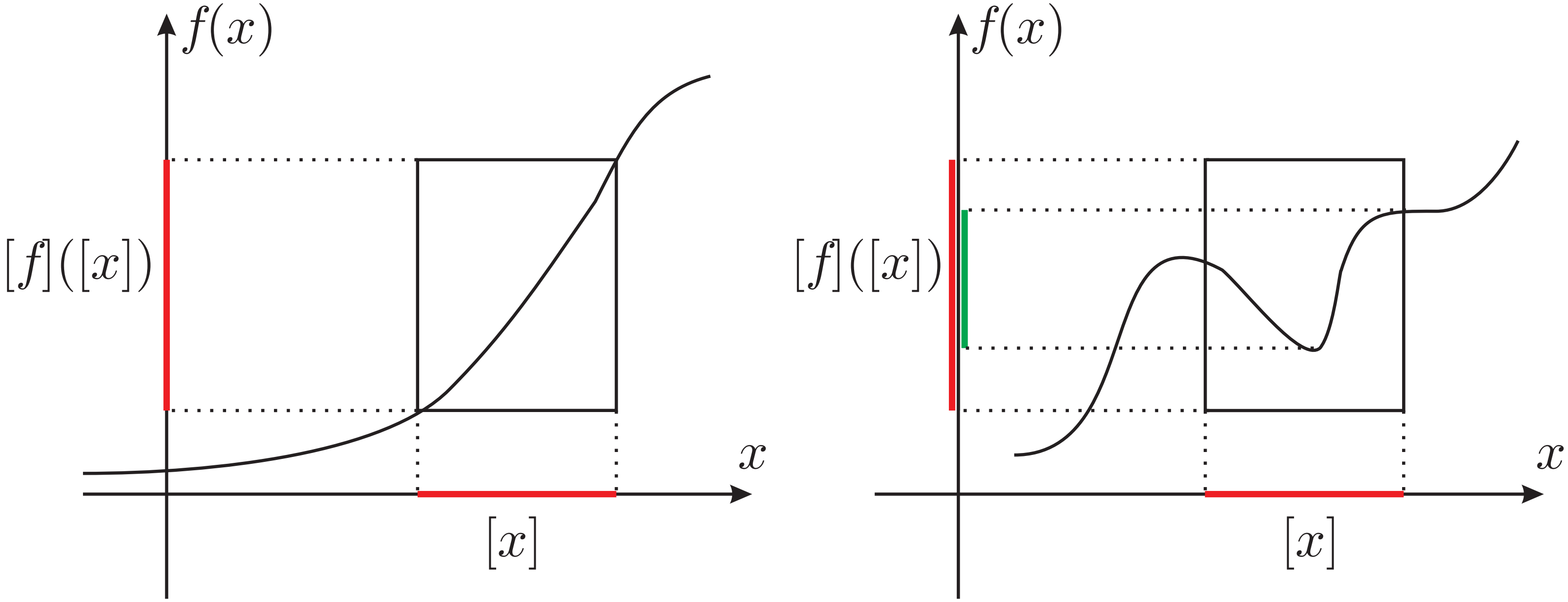
$$\begin{aligned}\sqrt{[x]} &= \left[\sqrt{\underline{x}}, \sqrt{\overline{x}}\right], \text{ si } \underline{x} \geq 0, \\ \exp([x]) &= [\exp(\underline{x}), \exp(\overline{x})], \\ \tan([x]) &= [\tan(\underline{x}), \tan(\overline{x})], \text{ if } [x] \subseteq [-\pi/2, \pi/2].\end{aligned}$$

More complicated for other elementary functions

$\Longrightarrow$ algorithm required for $\sin, \cos, \ldots$

$\Longrightarrow$ natural inclusion function

Usually, an inclusion function is not minimal



$\Longrightarrow$ some overestimation of the range (*pessimism*).

Natural inclusion function

$\Downarrow$

Remplace each real variable by its interval counterpart

$$x \longrightarrow [x]$$

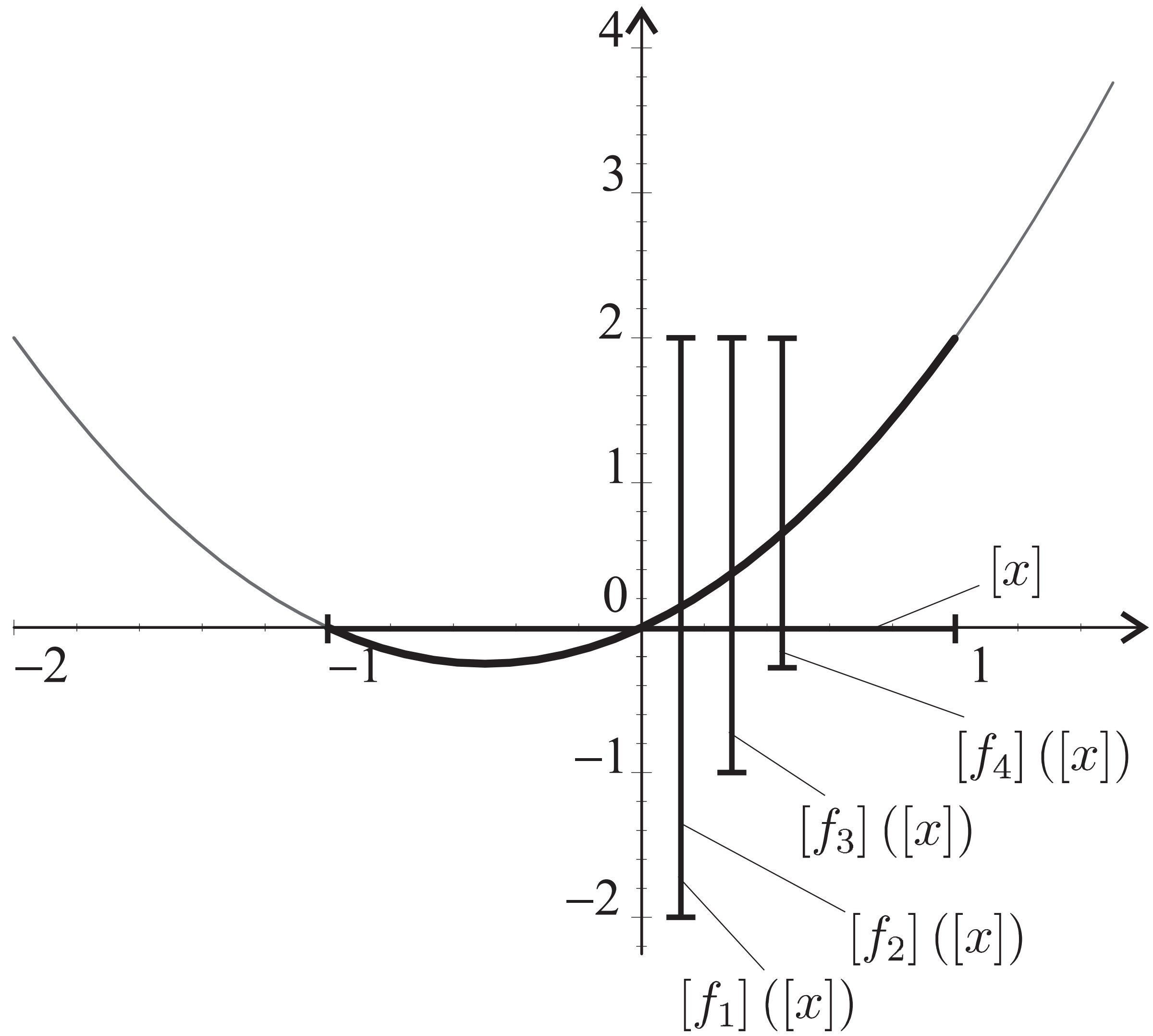
1.1.4 Example

$$f_1(x) = x(x+1), \qquad f_3(x) = x^2 + x,$$
$$f_2(x) = x \times x + x, \quad f_4(x) = (x + \tfrac{1}{2})^2 - \tfrac{1}{4}.$$

Results for $[x] = [-1, 1]$

$$\begin{aligned}
[f_1]([x]) &= [x]([x]+1) = [-2,2], \\
[f_2]([x]) &= [x] \times [x] + [x] = [-2,2], \\
[f_3]([x]) &= [x]^2 + [x] = [-1,2], \\
[f_4]([x]) &= \left([x] + \tfrac{1}{2}\right)^2 - \tfrac{1}{4} = \left[-\tfrac{1}{4}, 2\right].
\end{aligned}$$

Only $[f_4](.)$ is minimal $\Longleftrightarrow$ minimum number of occurences of the interval variable



4
3
2
1
0
−1
−2
−2
−1
1
$[x]$
$[f_4]([x])$
$[f_3]([x])$
$[f_2]([x])$
$[f_1]([x])$

1.1.5 Centred form

For $f : \mathcal{D} \longrightarrow \mathbb{R}$, differentiable over $[x] \subset \mathcal{D}$, one has $\forall x, m \in [x]\,,\ \exists \xi \in [x]$ such that

$$f\left(x\right) = f\left(m\right) + \left(x - m\right) f'\left(\xi\right).$$

Then

$$f\left(x\right) \in f\left(m\right) + \left(x - m\right) f'\left(\left[x\right]\right),$$

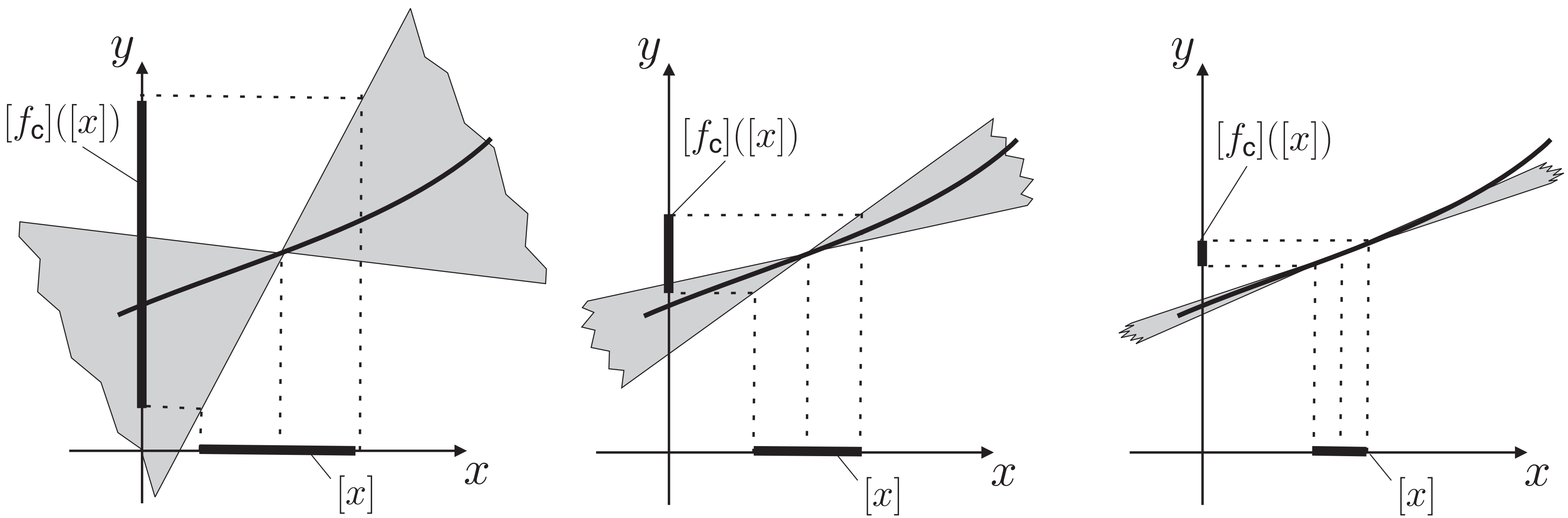
and

$$f\left(\left[x\right]\right) \subseteq f\left(m\right) + \left(\left[x\right] - m\right) \left[f'\right] \left(\left[x\right]\right).$$

Centred form is the inclusion function defined by

$$\left[f\right]_{\mathrm{c}} \left(\left[x\right]\right) = f\left(m\right) + \left(\left[x\right] - m\right) \left[f'\right] \left(\left[x\right]\right)$$

Interpretation of the centred form



1.1.6 Example

Consider

$$f(x) = x^2 \exp(x) - x \exp\left(x^2\right).$$

Compar the natural inclusion fonction and the centred form

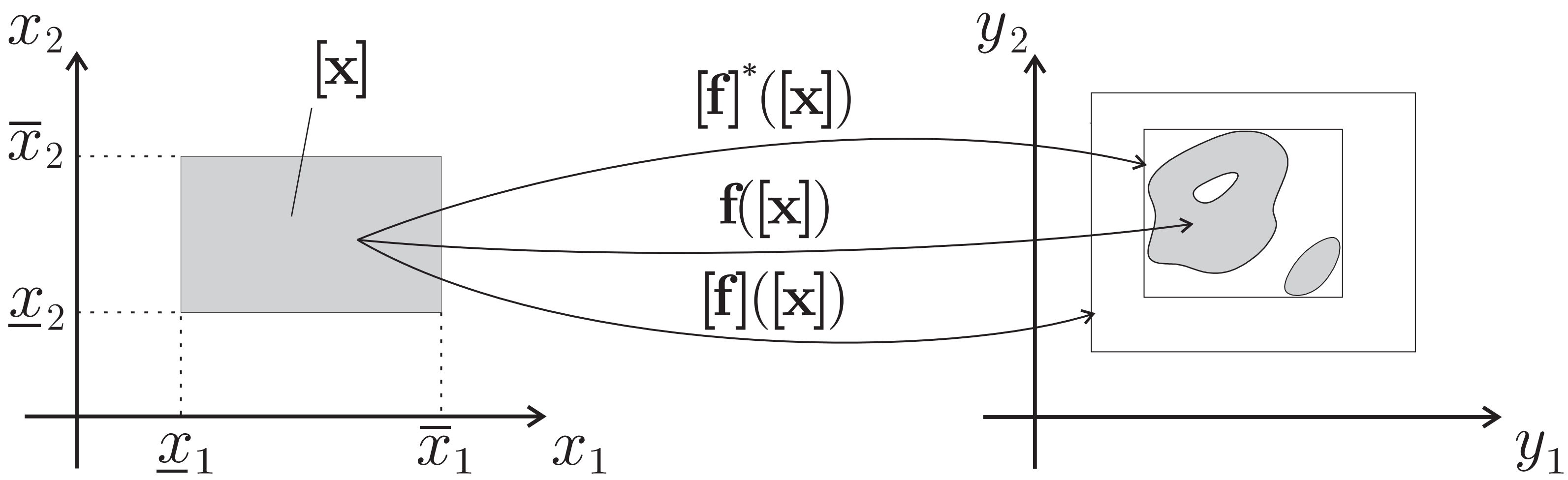
$[x]$	$f([x])$	$[f]([x])$	$[f]_c([x])$
$[0.5, 1.5]$	$[-4.148, 0]$	$[-13.82, 9.44]$	$[-25.07, 25.07]$
$[0.9, 1.1]$	$[-0.05380, 0]$	$[-1.697, 1.612]$	$[-0.5050, 0.5050]$
$[0.99, 1.01]$	$[-0.0004192, 0]$	$[-0.1636, 0.1628]$	$[-0.004656, 0.004656]$

1.1.7 Extension to vectors of intervals

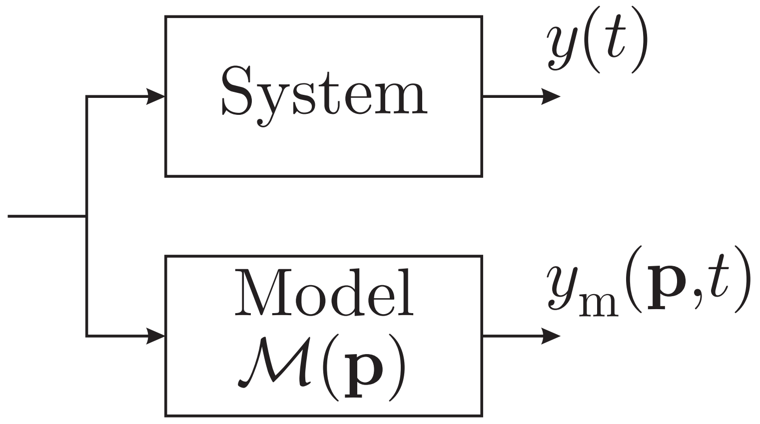
Vector of intervals or *box*

$$[\mathbf{x}] = [x_1] \times \cdots \times [x_n] \, .$$

Vector inclusion function



2 Parameter estimation



$\mathbf{y}$: vector of experimental data

$\mathbf{p}$: vector of unknown, constant parameters

$\mathbf{y}_m(\mathbf{p})$: vector of model output

Parameter estimation :

Determination of $\widehat{\mathbf{p}}$ from $\mathbf{y}$.

2.1 Problem formulation

1. Minimisation of a cost function, *e.g.*,

$$\widehat{\mathbf{p}} = \arg\min_{\mathbf{p}} j\left(\mathbf{p}\right) = \left(\mathbf{y} - \mathbf{y}_{\mathrm{m}}\left(\mathbf{p}\right)\right)^{\mathrm{T}}\left(\mathbf{y} - \mathbf{y}_{\mathrm{m}}\left(\mathbf{p}\right)\right)$$

   - Local techniques : Gauss-Newton, Levenberg-Marquardt...
   - Random search : simulated annealing, genetic algorithms...
   - Global guaranteed techniques : Hansen's algorithm

2.

2.2 Parameter bounding

Experimental data : $y(t_i)$,

t_i, $i = 1 \ldots, N$, known measurement times

$[\varepsilon_i] = [\underline{\varepsilon}_i, \overline{\varepsilon}_i]$, $i = 1, \ldots, N$, known acceptable errors

$\mathbf{p} \in \mathcal{P}_0$ deemed acceptable if for all $i = 1, \ldots, N$,

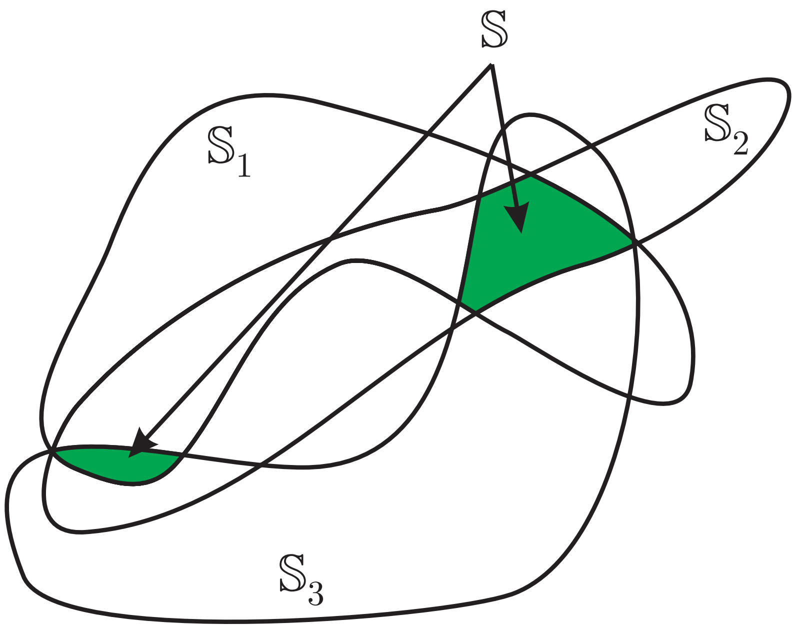
$$\underline{\varepsilon}_i \leqslant y(t_i) - y_{\mathrm{m}}(\mathbf{p}, t_i) \leqslant \overline{\varepsilon}_i.$$

$\Longrightarrow$ Bounded-error parameter estimation :

Characterize $\mathbb{S} = \{\mathbf{p} \in \mathcal{P}_0 \mid y(t_i) - y_{\mathrm{m}}(\mathbf{p}, t_i) \in [\underline{\varepsilon}_i, \overline{\varepsilon}_i], \; i = 1, \ldots, N\}$

- When $y_{\mathrm{m}}(\mathbf{p}, t_i)$ is linear in $\mathbf{p}$
  - exact description by polytopes
    (Walter and Piet-Lahanier, 1989…)
  - outer approximation by ellipsoids, polytopes, ...
    (Schweppe, 1973 ; Fogel ang Huang, 1982…)
- When $y_{\mathrm{m}}(\mathbf{p}, t_i)$ is non-linear in $\mathbf{p}$
  - outer approximation by polytopes, ellipsoids…
    (Norton, 1987 ; Clément and Gentil, 1988 ; Cerone, 1991...)
  - approximate but guaranteed enclosure of $\mathcal{S}$ by Sivia
    (Moore, 1992 ; Jaulin and Walter 1993)

2.3 Robust parameter bounding



$$\mathbb{S} = \bigcap_{\ell=1\ldots N} \mathbb{S}_\ell,$$

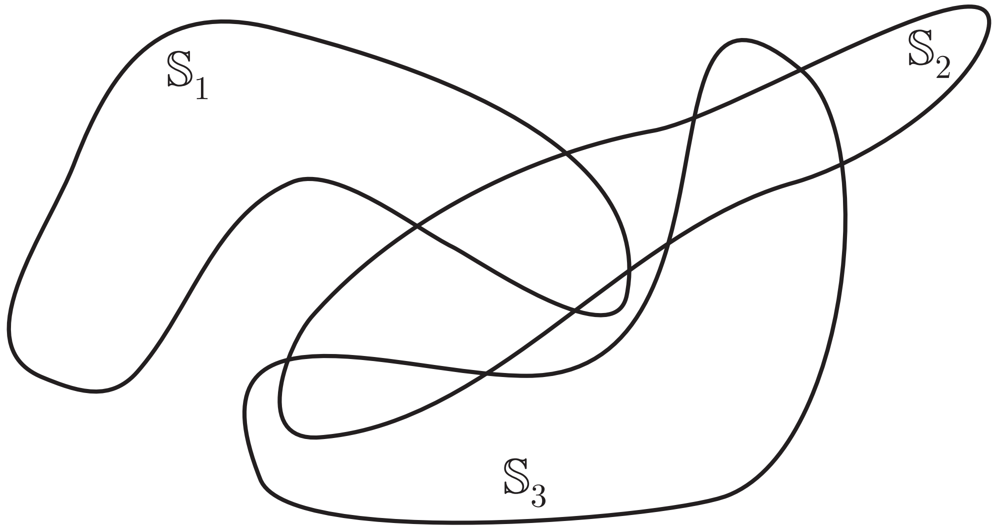
avec

$$\mathbb{S}_\ell = \{\mathbf{p} \in \mathcal{P}_0 \mid y_\ell^{\mathrm{m}}(\mathbf{p}) - y_\ell \in [\underline{\varepsilon}_\ell, \overline{\varepsilon}_\ell]\}$$

Interval analysis [**?**, **?**], [?] allows to get

$$\underline{\mathbb{S}} \subset \mathbb{S} \subset \overline{\mathbb{S}}$$

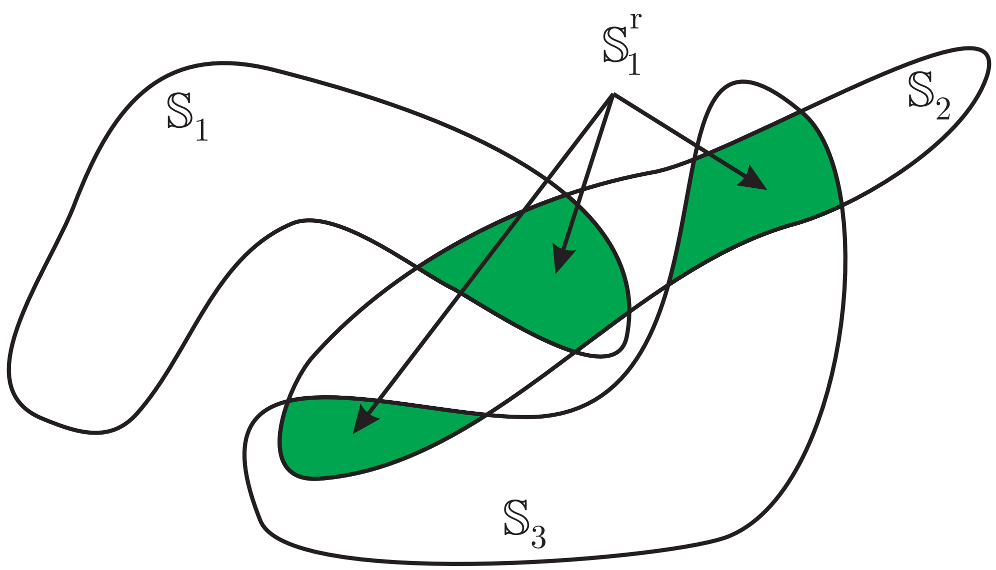
No consistent **p** is missed $\Longrightarrow$ guaranteed set estimate.



When the solution set is empty

$$\mathbb{S} = \bigcap_{\ell=1\ldots N} \mathbb{S}_\ell = \emptyset.$$

Hypothesis on model or noise violated



Estimator robust against n outliers

$$\mathbb{S}_n^{\mathrm{r}} = \bigcup_{1 \leqslant \ell_1 < \cdots < \ell_n \leqslant N} \ \bigcap_{\ell \neq \ell_1, \ldots, \ell \neq \ell_N} \mathbb{S}_\ell .$$

Intersection of $N - n$ sets among N

Interval analysis $\Longrightarrow$ non-combinatorial solution

$$\mathbb{S}_n^{\mathrm{r}} = \left\{ \mathbf{p} \in \mathcal{P}_0 \mid \sum_{\ell=1}^{N} t_\ell (\mathbf{p}) \geq N - n \right\}$$

with

$$t_\ell (\mathbf{p}) = \left(y_\ell^{\mathrm{m}} (\mathbf{p}) - y_\ell \in [\underline{\varepsilon}_\ell, \overline{\varepsilon}_\ell] \right)$$

$\mathbb{S}_n^{\mathrm{r}}$ evaluated with a complexity similar to that of $\mathbb{S}$

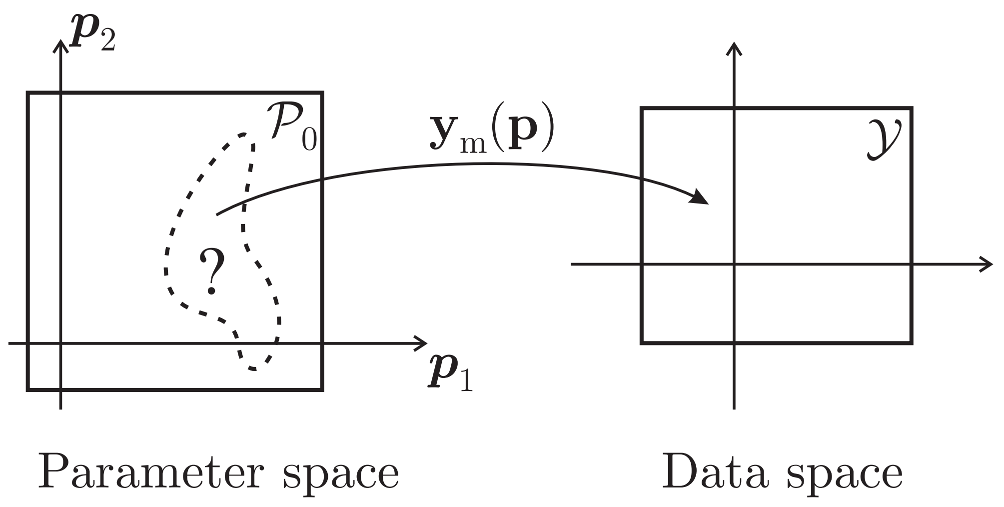
2.4 Sivia

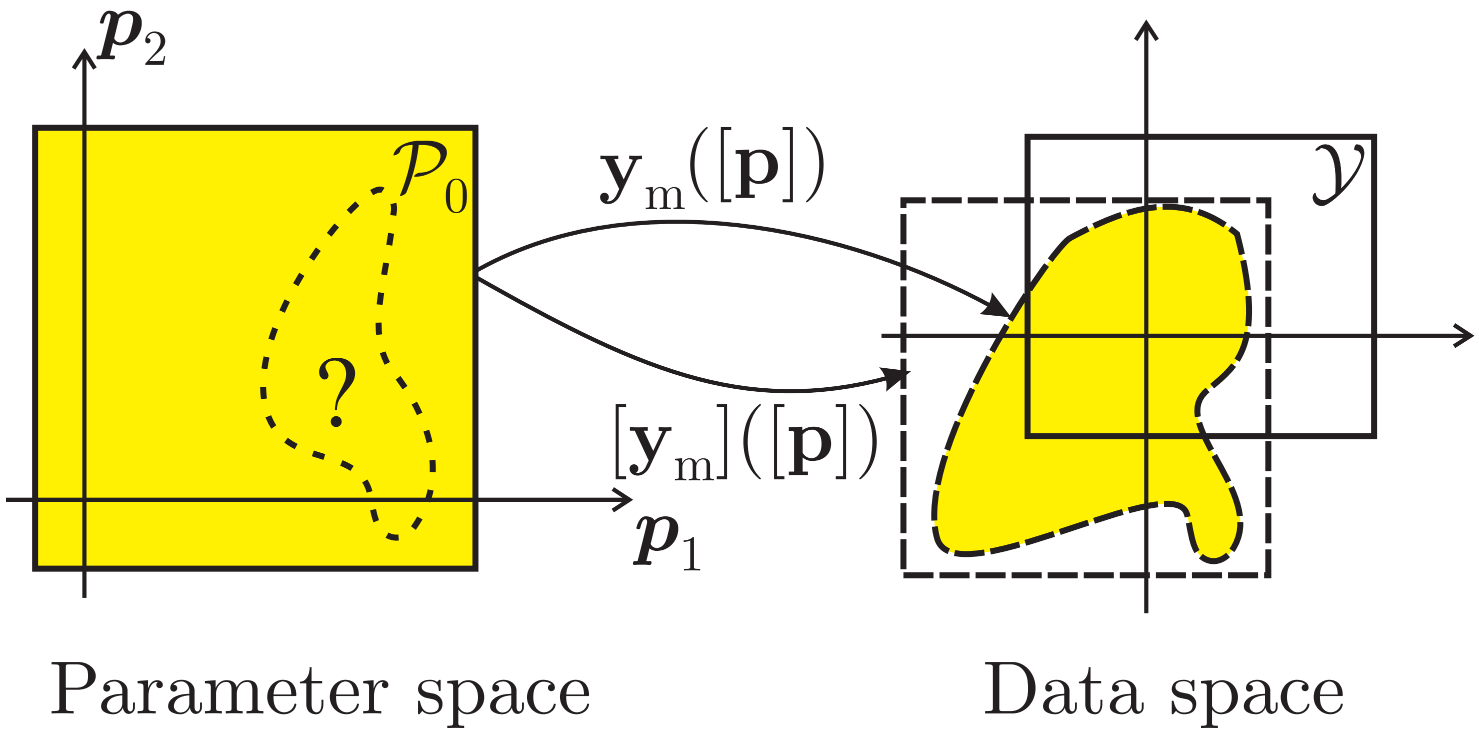
Set to be characterized

$$\begin{aligned}\mathbb{S} &= \{\mathbf{p} \in \mathcal{P}_0 \mid y\left(t_i\right) - y_{\mathrm{m}}\left(\mathbf{p}, t_i\right) \in \left[\underline{\varepsilon}_i, \overline{\varepsilon}_i\right], i = 1, \ldots, N\} \\ &= \{\mathbf{p} \in \mathcal{P}_0 \mid \mathbf{y}_{\mathrm{m}}\left(\mathbf{p}\right) \subset \mathcal{Y}\},\end{aligned}$$

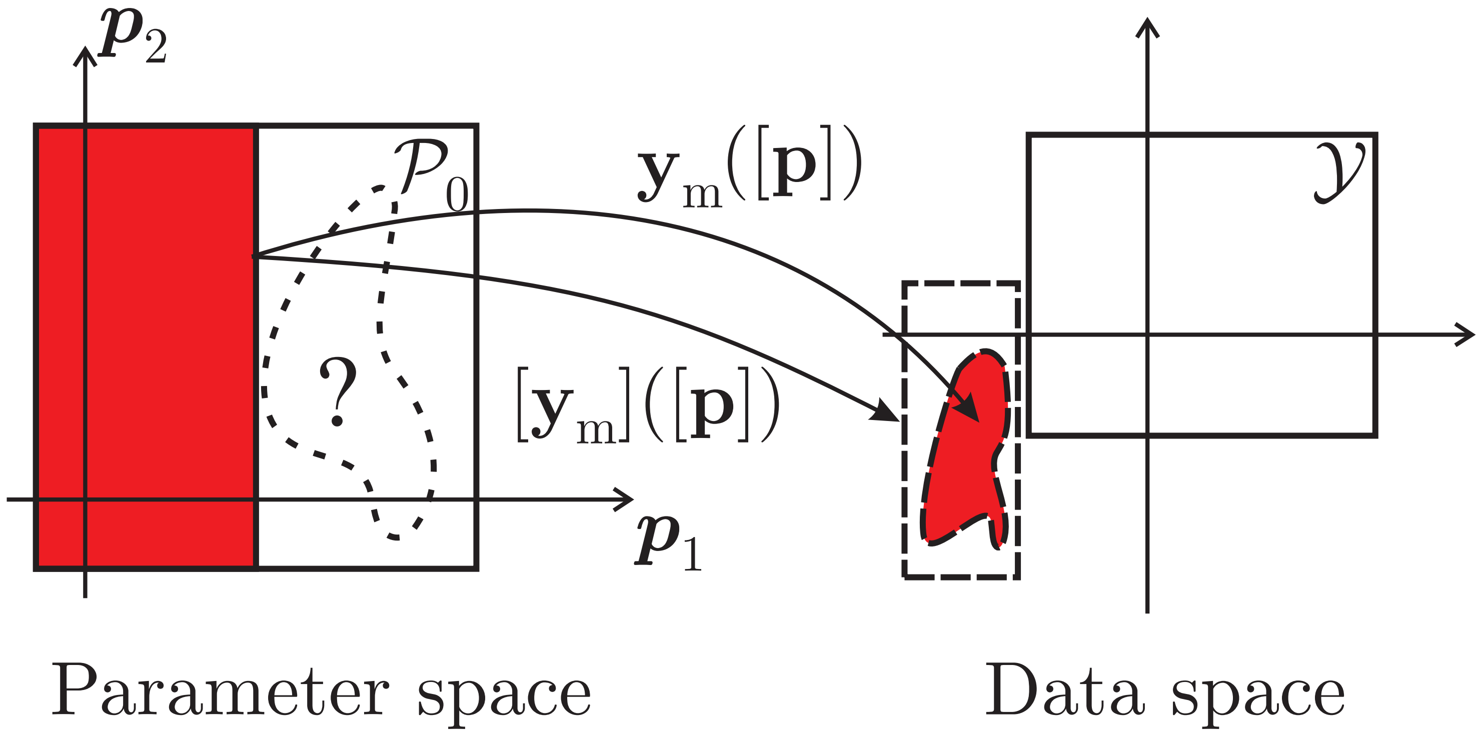
with

$$\mathcal{Y} = [y(t_1) - \overline{\varepsilon}_1, y\left(t_1\right) - \underline{\varepsilon}_1] \times \cdots \times [y(t_N) - \overline{\varepsilon}_N, y\left(t_N\right) - \underline{\varepsilon}_N]$$

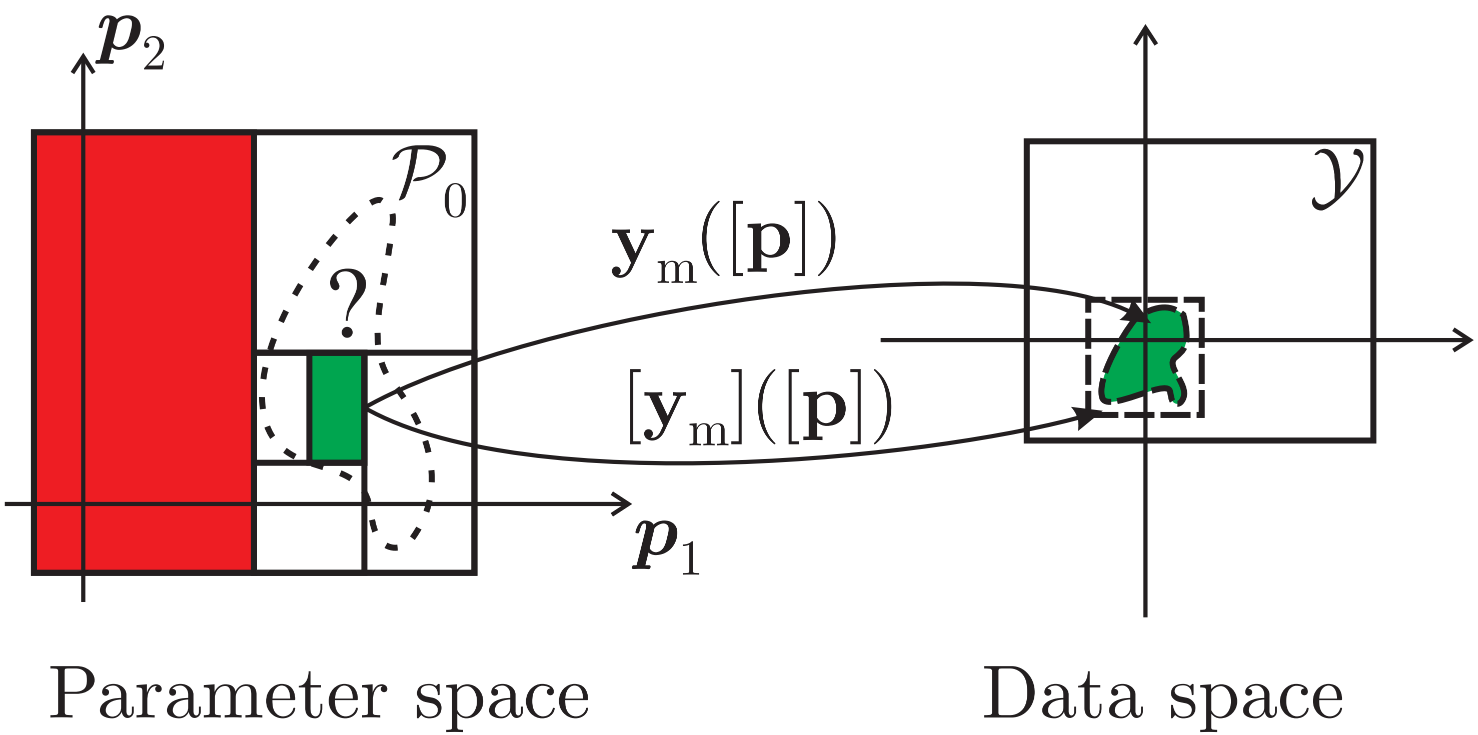




Yellow box is undetermined



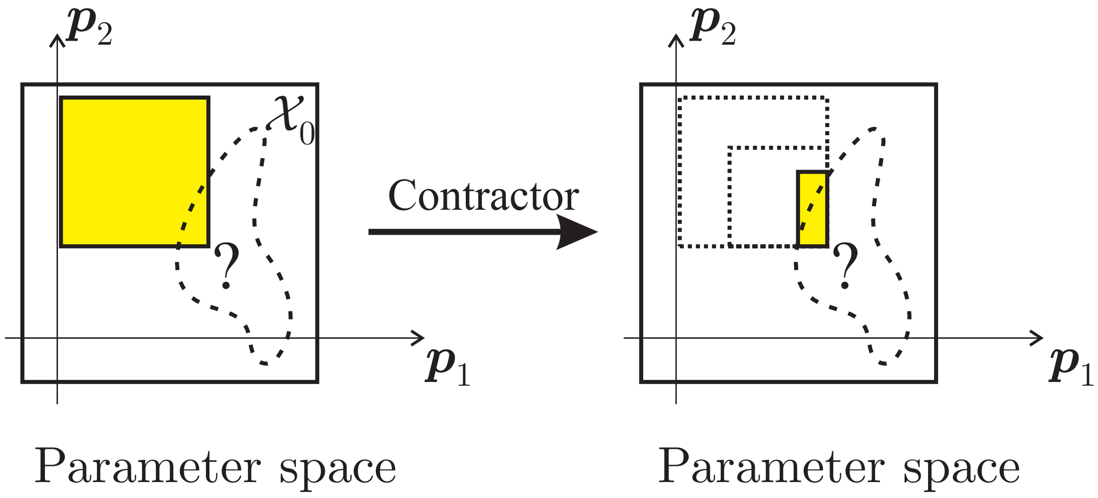
Red box proven to be outside $\mathcal{S}$



Green box proven to be included in $\mathcal{S}$

2.5 Sivia with contractors

Reduce the size of undetermined boxes without any bisection



Contractors (Jaulin *et al*, 2001) based on

- interval constraint propagation
- linear programming
- parallel linearization
- ...

Example of interval constraint propagation

$$y_{\mathrm{m}}(\mathbf{p}) = p_1 \exp(-p_2),$$

$$p_1 \in [p_1]^0 = [-2, 2], \; p_2 \in [p_2]^0 = [-2, 2].$$

One want to characterise the set

$$\mathcal{S} = \left\{ \mathbf{p} \in [p_1]^0 \times [p_2]^0 \mid \mathbf{y}_{\mathrm{m}}(\mathbf{p}) \subset [1, 2] \right\}.$$

One may write that

$$p_1 \exp(-p_2) \in [1, 2],$$

thus

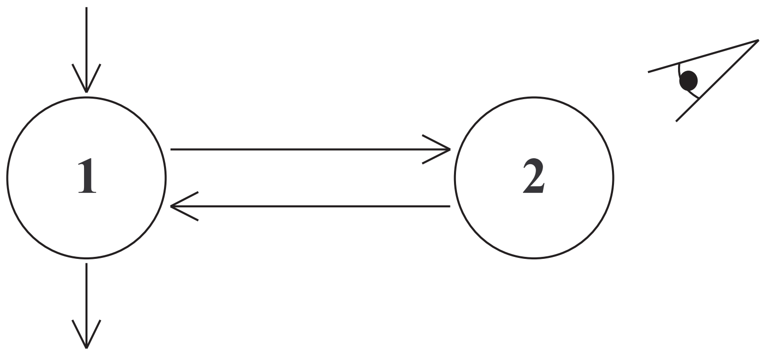
$$\begin{aligned} p_1 &\in [-2, 2] \cap \left(\frac{[1, 2]}{\exp([-2, 2])} \right) = [-2, 2] \cap [0.1353, 14.78] \\ &\in \color{red}{[0.1353, 2]}. \end{aligned}$$

Similarly for p_2, one has

$$\begin{aligned} p_2 &\in [-2, 2] \cap \left(-\ln \left(\frac{[1, 2]}{[0.1353, 2]} \right) \right) = [-2, 2] \cap [-2.6932, 0.6932] \\ &\in \color{red}{[-2, 0.6932]} \end{aligned}$$

2.6 Example

Estimation of the parameters of a compartmental model



State equation

$$\left\{\begin{array}{l} x_1' = -\left(k_{01}+k_{21}\right)x_1 + k_{12}x_2 \\ x_2' = k_{21}x_1 - k_{12}x_2 \end{array}\right. \quad \text{with} \quad \left\{\begin{array}{l} x_1\left(0\right) = 0 \\ x_2\left(0\right) = 0 \end{array}\right.$$

Observation equation

$$y\left(t_i\right) = x_2\left(t_i\right) + b\left(t_i\right),\ \ i = 1, \ldots, 16$$

Model

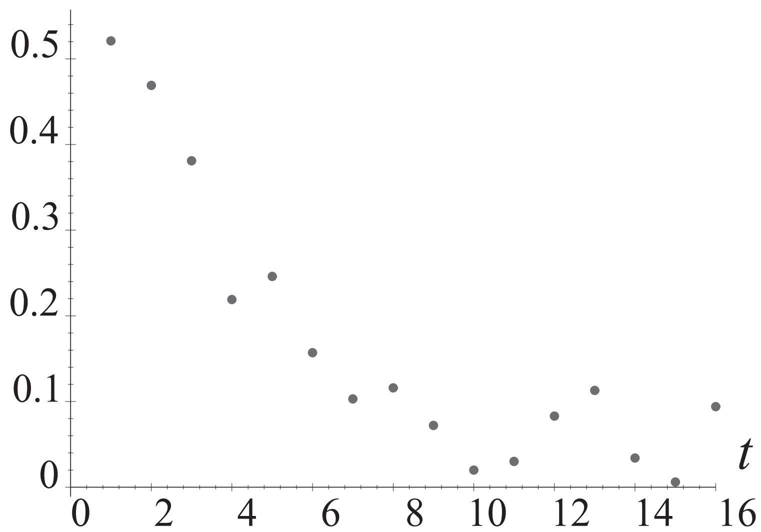
$$y_{\mathrm{m}}\left(\mathbf{p}, t_i\right) = p_1\left(\exp\left(p_2 t_i\right) - \exp\left(p_3 t_i\right)\right), \;\; i = 1, \ldots, 16,$$

where the macroparameters

$$\mathbf{p} = \left(p_1, p_2, p_3\right)^{\mathrm{T}}$$

depends on the microparameters

$$\left(k_{01}, k_{12}, k_{21}\right).$$



Simulated
noisy experimental data

Macroparameter estimation with

$$\underline{\varepsilon}_i = -0.09,\ \overline{\varepsilon}_i = 0.09,\ i = 1, \ldots, 16$$

Results

	SIVIA	SIVIA + ICP	ICP only
Comp. time (s)	8	6.2	0.63
Bounding box	$[0.49, 1.06]$ $[-0.293, -0.141]$ $[-5, -1.054]$	$[0.49, 1.06]$ $[-0.293, -0.141]$ $[-5, -1.054]$	$[0.52, 0.98]$ $[-0.282, -0.156]$ $[-5, -1.167]$

2.7 Limitations

To test $[\mathbf{p}]$, Sivia evaluates $[y_{\mathrm{m}}]([\mathbf{p}], t_i)$, $i = 1, \ldots, 16$:

- explicit expression of $y_{\mathrm{m}}(\mathbf{p}, t_i)$ required
- if available, can be complicated, *e.g.*, here

$$y_{\mathrm{m}}(\mathbf{p}, t_i) = \frac{k_{21}}{\sqrt{(k_{01} - k_{12} + k_{21}) + 4k_{12}k_{21}}} \times \left(\exp\left(-\left((k_{01} + k_{12} + k_{21}) + \sqrt{(k_{01} - k_{12} + k_{21}) + 4k_{12}k_{21}}\right)\frac{t_i}{2}\right) - \exp\left(-\left((k_{01} + k_{12} + k_{21}) - \sqrt{(k_{01} - k_{12} + k_{21}) + 4k_{12}k_{21}}\right)\right)\frac{t_i}{2}\right)$$

$\hookrightarrow$ multiple occurences

$\hookrightarrow$ non-minimal inclusion functions

2.8 Alternative approach

Guaranteed numerical integration of state equation

State equation

$$\mathbf{x}' = \frac{d\mathbf{x}}{dt} = \mathbf{f}\left(\mathbf{x}, \mathbf{p}^*, \mathbf{w}, \mathbf{u}\right),$$

where

$\mathbf{w}$: state perturbation assumed bounded,

$\mathbf{u}$: known input.

Observation equation

$$\mathbf{y}\left(t_i\right) = \mathbf{h}\left(\mathbf{x}\left(\mathbf{p}^*, t_i\right)\right) + \mathbf{v}\left(t_i\right), \; i = 1, \ldots, N,$$

where

$\mathbf{v}$: measurement noise assumed bounded.

Example of model output

$$\mathbf{y}_{\mathrm{m}}(\mathbf{p}, t_i) = \mathbf{h}(\mathbf{x}(\mathbf{p}, t_i)), \; i = 1, \ldots, N.$$

Sivia requires tight enclosure of $\mathbf{y}_{\mathrm{m}}([\mathbf{p}], t_i)$

$\Rightarrow$ integration of dynamical system with large $[\mathbf{p}]$

$\hookrightarrow$ important wrapping effect

$\hookrightarrow$ pessimism introduced

For general models, guaranteed numerical integration not adapted.

But can be used for cooperative systems.

2.9 Parameter estimation for cooperative systems

Tight enclosures of $\mathbf{y}_{\mathrm{m}}([\mathbf{p}], t_i)$ easily obtained for cooperative systems.

Definition 1 *(Smith, 94) The dynamical system*

$$\mathbf{x}' = \mathbf{f}(\mathbf{x}, t),$$

where $\mathbf{f}(\mathbf{x}, t)$ *is continuous and differentiable is cooperative on a domain* $\mathcal{D}$ *if*

$$\frac{\partial f_i}{\partial x_j} \geqslant 0, \text{ for any } i \neq j, \; t \geqslant 0 \text{ and } \mathbf{x} \in \mathcal{D}.$$

Theorem 1 *(Smith, 94) Consider the system*

$$\mathbf{x}' = \frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}, \mathbf{p}, \mathbf{w}, \mathbf{u}).$$

If there exists a pair of cooperative systems

$$\begin{cases} \mathbf{x}' = \underline{\mathbf{f}}(\mathbf{x},t) \\ \mathbf{x}' = \overline{\mathbf{f}}(\mathbf{x},t) \end{cases}$$

satisfying

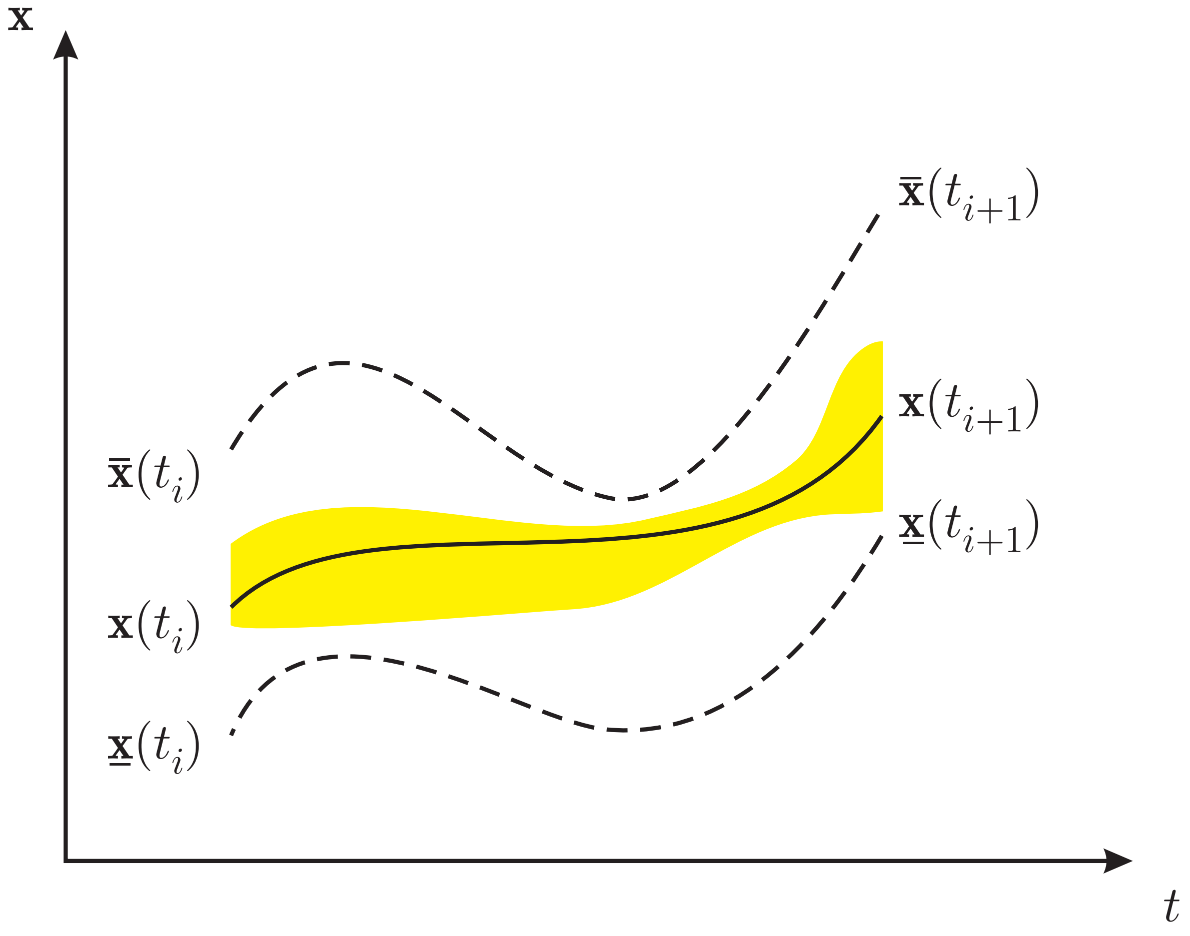
- $\underline{\mathbf{f}}(\mathbf{x},t) \leqslant \mathbf{f}(\mathbf{x}, \mathbf{p}, \mathbf{w}, \mathbf{u}) \leqslant \overline{\mathbf{f}}(\mathbf{x},t)$,
  for any $\mathbf{p} \in \left[\underline{\mathbf{p}}, \overline{\mathbf{p}}\right]$, $\mathbf{w} \in [\underline{\mathbf{w}}(t), \overline{\mathbf{w}}(t)]$, $t \geqslant 0$ *and* $\mathbf{x} \in \mathcal{D}$,
- $\underline{\mathbf{x}}_0 \leqslant \mathbf{x}(0) \leqslant \overline{\mathbf{x}}_0$,

then

$$\underline{\mathbf{x}}(t) \leqslant \mathbf{x}(t) \leqslant \overline{\mathbf{x}}(t), \text{ for any } t \geqslant 0,$$

with

- $\underline{\mathbf{x}}(t) = \underline{\phi}(\underline{\mathbf{x}}_0, t)$ *the flow corresponding to* $\{\underline{\mathbf{x}}' = \underline{\mathbf{f}}(\underline{\mathbf{x}},t), \underline{\mathbf{x}}(0) = \underline{\mathbf{x}}_0\}$
- $\overline{\mathbf{x}}(t) = \overline{\phi}(\overline{\mathbf{x}}_0, t)$ *the flow corresponding to* $\left\{\overline{\mathbf{x}}' = \overline{\mathbf{f}}(\overline{\mathbf{x}},t), \overline{\mathbf{x}}(0) = \overline{\mathbf{x}}_0\right\}$.


$\mathbf{x}$
$\overline{\mathbf{x}}(t_{i+1})$
$\mathbf{x}(t_{i+1})$
$\underline{\mathbf{x}}(t_{i+1})$
$\overline{\mathbf{x}}(t_i)$
$\mathbf{x}(t_i)$
$\underline{\mathbf{x}}(t_i)$
t

Steps to build an inclusion function for $\mathbf{y}_{\mathrm{m}}([\mathbf{p}], t_i)$

1. Find a pair of cooperative systems satisfying

$$\underline{\mathbf{f}}(\mathbf{x},t) \leqslant \mathbf{f}(\mathbf{x},\mathbf{p},\mathbf{w},\mathbf{u}) \leqslant \overline{\mathbf{f}}(\mathbf{x},t),$$

for all $\mathbf{p} \in [\underline{\mathbf{p}}, \overline{\mathbf{p}}]$, $\mathbf{w} \in [\underline{\mathbf{w}}(t), \overline{\mathbf{w}}(t)]$, $t \geqslant 0$ and $\mathbf{x} \in \mathcal{D}$.

2. Integrate

$$\begin{cases} \underline{\mathbf{x}}' = \underline{\mathbf{f}}(\underline{\mathbf{x}},t) \\ \overline{\mathbf{x}}' = \overline{\mathbf{f}}(\overline{\mathbf{x}},t) \end{cases} \text{with} \begin{cases} \underline{\mathbf{x}}(0) = \underline{\mathbf{x}}_0 \\ \overline{\mathbf{x}}(0) = \overline{\mathbf{x}}_0 \end{cases}$$

with guaranteed ODE solvers to get

$$\begin{cases} [\underline{\phi}(\underline{\mathbf{x}}_0, t_i)] = \left[\underline{\underline{\phi}(\underline{\mathbf{x}}_0, t_i)}, \overline{\underline{\phi}(\underline{\mathbf{x}}_0, t_i)}\right] \\ [\overline{\phi}(\overline{\mathbf{x}}_0, t_i)] = \left[\underline{\overline{\phi}(\overline{\mathbf{x}}_0, t_i)}, \overline{\overline{\phi}(\overline{\mathbf{x}}_0, t_i)}\right] \end{cases}, \quad i = 1, \ldots, N$$

3. The box-valued function

$$[[\phi]]([\mathbf{x}], t_i) = \left[\underline{\underline{\phi}(\underline{\mathbf{x}}, t)}, \overline{\overline{\phi}(\overline{\mathbf{x}}, t_i)}\right]$$

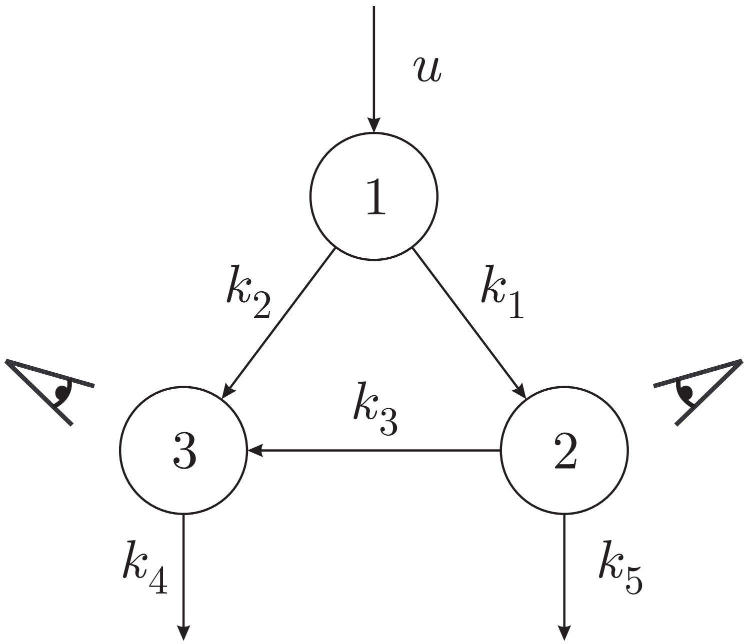
is an inclusion function for $\mathbf{x}(t_i)$

and the box-valued function

$$[\mathbf{h}]\left([[\phi]]\left([\mathbf{x}], t_i\right)\right)$$

is thus an inclusion function for $\mathbf{y}_{\mathrm{m}}\left([\mathbf{p}], t_i\right)$.

2.10 Example



Compartmental model
of the behaviour of a drug
(Glafenine) administered orally.

$$\begin{cases} x_1' = -(k_1 + k_2)x_1 + u \\ x_2' = k_1 x_1 - (k_3 + k_5)\, x_2 \\ x_3' = k_2 x_1 + k_3 x_2 - k_4 x_3 \end{cases}$$

$$\mathbf{y}_{\mathrm{m}}(\mathbf{p},t) = \left(x_2(\mathbf{p},t)\,,\; x_3(\mathbf{p},t)\right)^{\mathrm{T}}.$$

Unknown parameter vector $\mathbf{p}^* = (k_1, k_2, k_3, k_4, k_5)^{\mathrm{T}}$, with $\mathbf{p}^* > \mathbf{0}$.

Can be bounded between

$$\left\{\begin{aligned} \underline{x}_1' &= -(\overline{k}_1 + \overline{k}_2)\underline{x}_1 + u \\ \underline{x}_2' &= \underline{k}_1\underline{x}_1 - \left(\overline{k}_3 + \overline{k}_5\right)\underline{x}_2 \\ \underline{x}_3' &= \underline{k}_2\underline{x}_1 + \underline{k}_3\underline{x}_2 - \overline{k}_4\underline{x}_3 \end{aligned}\right. \quad \text{and} \quad \left\{\begin{aligned} \overline{x}_1' &= -(\underline{k}_1 + \underline{k}_2)\overline{x}_1 + u \\ \overline{x}_2' &= \overline{k}_1\overline{x}_1 - (\underline{k}_3 + \underline{k}_5)\,\overline{x}_2 \\ \overline{x}_3' &= \overline{k}_2\overline{x}_1 + \overline{k}_3\overline{x}_2 - \underline{k}_4\overline{x}_3 \end{aligned}\right.$$

$\Longrightarrow$ two cooperative systems

Guaranteed numerical integration provides inclusion function for $\mathbf{y}_{\mathrm{m}}(\mathbf{p},t)$, here minimal.

Simulation conditions

$\mathbf{p}^* = (0.6,\ 0.8,\ 1,\ 0.2,\ 0.4)^{\mathrm{T}}$

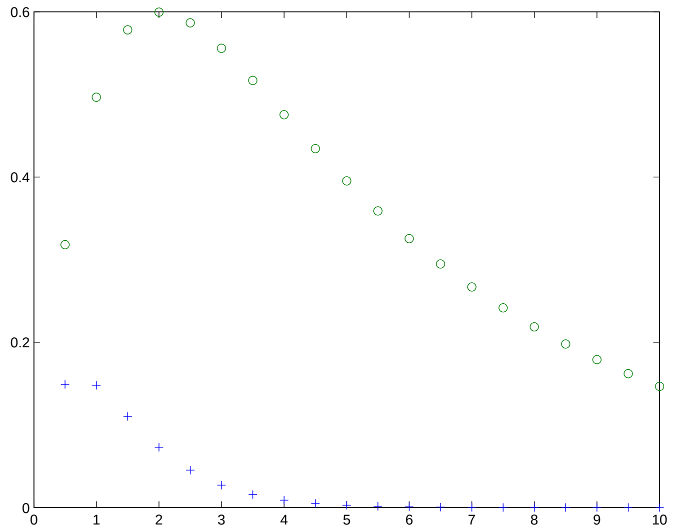
Imput $u(t) = \delta(t)$

Outputs of Compartments 2 and 3 have been measured at $t_i = 0.5i$, $i = 1, \ldots, 20$.

Introduction of bounded relative random noise

$$\widetilde{y}_i \to y_i (1 + \epsilon_i)$$

with ϵ_i random in $[-0.01,\ 0.01]$.



Compartment 2 (+)
Compartment 3 (o)

Solution

Precision parameter : $\epsilon = 0.01$

Computing time : 15 mn on an Athlon 1800

Bounding box :

$$\mathcal{S} \subset [0.586, 0.625] \times [0.74, 0.85]$$
$$\times [0.81, 1.25] \times [0.185, 0.215] \times [0.235, 0.56]$$

contains $\mathbf{p}^*$.

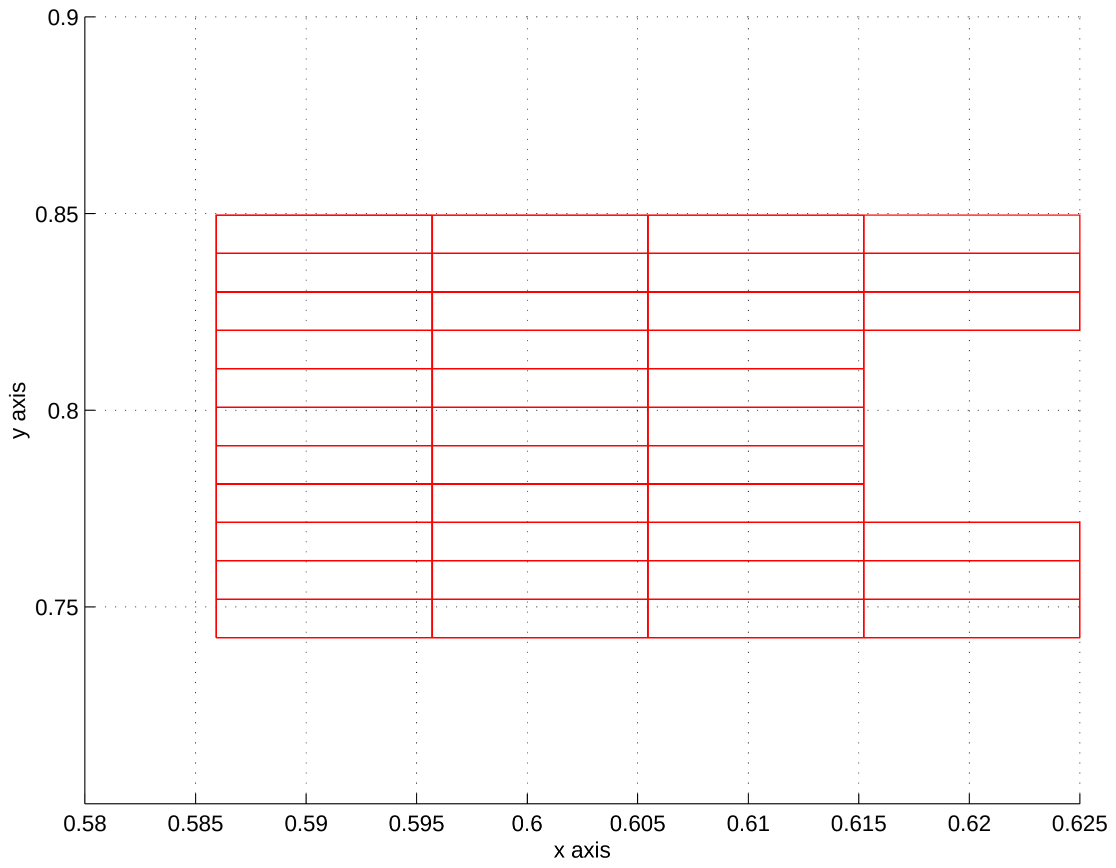


Figure 1: Projection onto the $(k_1,\ k_2)$ −plane

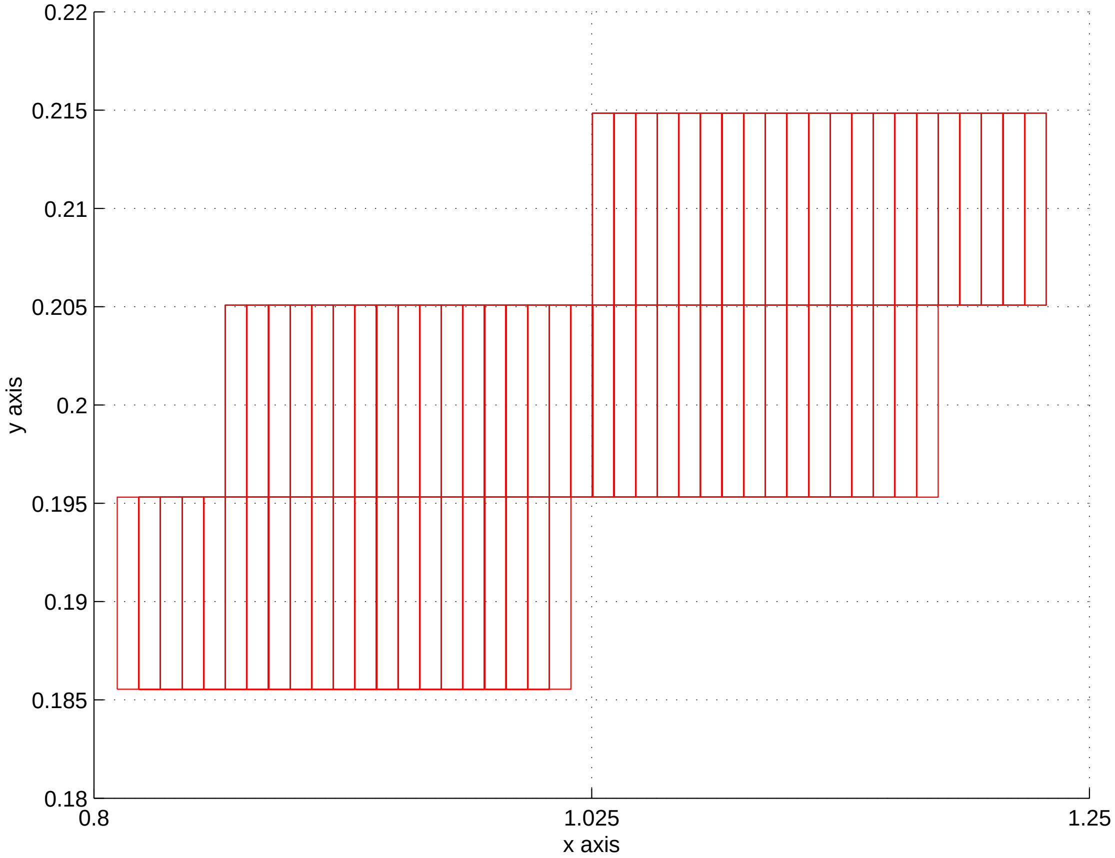


Figure 2: projection onte the $(k_3,\ k_4)$ −plane

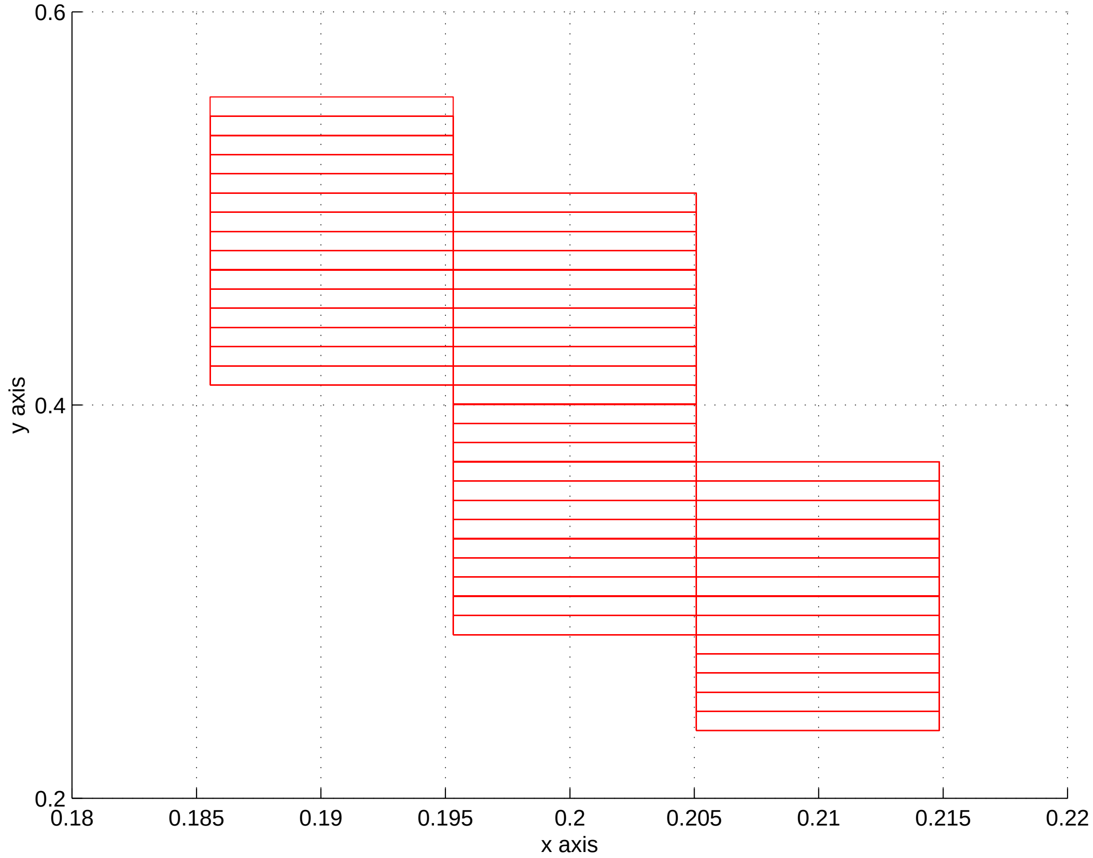


Figure 3: Projection onto the $(k_4,\ k_5)$ −plane

2.11 How contractors may be used again?

All values of the parameter vector $\mathbf{p} \in \mathbb{S}$ satisfy

$$\mathbf{y}_{\mathrm{m}}(\mathbf{p}) \in [\mathbf{y}] = \left[\underline{\mathbf{y}}, \overline{\mathbf{y}}\right],$$

which leads to

$$\left\{ \begin{array}{r} \mathbf{y}_{\mathrm{m}}(\mathbf{p}) - \underline{\mathbf{y}} \geqslant \mathbf{0} \\ -\mathbf{y}_{\mathrm{m}}(\mathbf{p}) + \overline{\mathbf{y}} \geqslant \mathbf{0} \end{array} \right. . \tag{1}$$

Centered form, for the model output: For the kth component $y_k^{\mathrm{m}}(\mathbf{p})$ of $\mathbf{y}_{\mathrm{m}}(\mathbf{p})$, for all $\mathbf{p} \in \mathbb{S} \subset [\mathbf{p}]$ and $\mathbf{m} \in [\mathbf{p}]$, (1) translates into

$$\left\{ \begin{array}{r} y_k^{\mathrm{m}}(\mathbf{m}) + \sum_{j=1}^{n_{\mathrm{p}}} ([p_j] - m_j) \left[\frac{\partial y_k^{\mathrm{m}}}{\partial p_j}\right]([\mathbf{p}]) - \underline{y}_k \geqslant 0, \\ -y_k^{\mathrm{m}}(\mathbf{m}) - \sum_{j=1}^{n_{\mathrm{p}}} ([p_j] - m_j) \left[\frac{\partial y_k^{\mathrm{m}}}{\partial p_j}\right]([\mathbf{p}]) + \overline{y}_k \geqslant 0, \end{array} \right.$$

for $k = 1, \ldots, \dim \mathbf{y}_{\mathrm{m}}(\mathbf{p})$.

Contracted domain $[\mathbf{p}]^{\text{new}} = C_k([\mathbf{p}])$, with components

$$[p_i]^{\text{new}} = [p_i] \cap \left(\left(\left[\underline{y}_k, \overline{y}_k \right] - y_k^{\text{m}}(\mathbf{m}) - \sum_{j \neq i} ([p_j] - m_j) \left[\frac{\partial y_k^{\text{m}}}{\partial p_j} \right] ([\mathbf{p}]) \right) / \left[\frac{\partial y_k^{\text{m}}}{\partial p_i} \right] ([\mathbf{p}]) + m_i \right) \tag{2}$$

for $i = 1, \ldots, n_{\text{p}}$.

Requires sensitivity function of the model output.

2.11.1 Sensitivity functions

First-order sensitivity of x_j with respect to p_k by

$$s_{jk}(\mathbf{p},t) = \frac{\partial x_j}{\partial p_k}(\mathbf{p},t)\,. \tag{3}$$

For model output is linear in state and given by

$$\mathbf{h}(\mathbf{x}(t),\mathbf{p}) = \mathbf{M}\mathbf{x}(t)\,, \tag{4}$$

where $\mathbf{M}$ is a known matrix. Jacobian matrix of $\mathbf{h}(\mathbf{x}(t),\mathbf{p})$ then given by

$$\mathbf{J}_h(\mathbf{p},t) = \mathbf{M}\frac{\partial \mathbf{x}(\mathbf{p},t)}{\partial \mathbf{p}}, \tag{5}$$

with

$$\frac{\partial \mathbf{x}(\mathbf{p},t)}{\partial \mathbf{p}} = \left(s_{jk}(\mathbf{p},t)\right), j = 1,\ldots,\dim \mathbf{x}, k = 1,\ldots,\dim \mathbf{p}. \tag{6}$$

To compute s_{jk}, differentiate the jth row of

$$\frac{d\mathbf{x}}{dt} = \mathbf{f}(\mathbf{x}, \mathbf{p}) \tag{7}$$

to get

$$s'_{jk} = \frac{\partial f_j(\mathbf{x}, \mathbf{p})}{\partial x_j} s_{jk} + \frac{\partial f_j(\mathbf{x}, \mathbf{p})}{\partial p_k}. \tag{8}$$

When $\mathbf{x}(t_0)$ is assumed to be known, the initial conditions are

$$s_{jk}(t_0) = \frac{\partial \mathbf{x}(t_0)}{\partial p_k} = 0.$$

Sensitivity function obtained by considering extended state-space model consisting of

- the dynamical part of (7),
- all differential equations (8) satisfied by the sensitivity functions.

2.11.2 Example

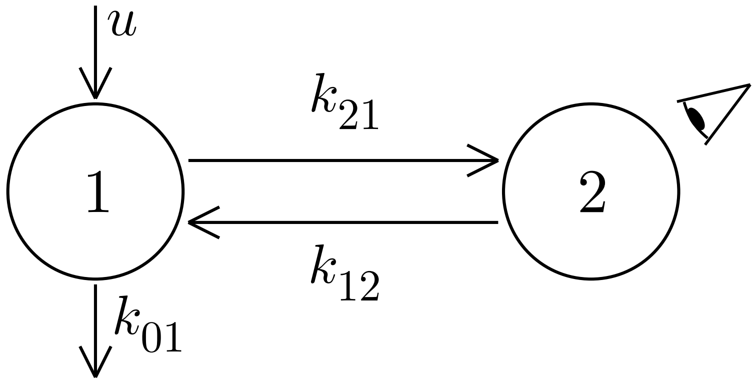


Figure 4: Two-compartment model

State equation obtained from conservation law as

$$\mathbf{x}' = \mathbf{f}\left(\mathbf{x}, \mathbf{p}, u\right), \tag{9}$$

where $\mathbf{p} = \left(k_{21}, k_{12}, k_{01}\right)^{\mathrm{T}}$ and

$$\mathbf{f}\left(\mathbf{x}, \mathbf{p}, u\right) = \begin{pmatrix} -\left(p_1 + p_3\right) x_1 + p_2 x_2 + u \\ p1 x_1 - p_2 x_2 \end{pmatrix}. \tag{10}$$

Quantity of material in Compartment 2 observed, so

$$y_{\mathrm{m}}\left(t_i, \mathbf{p}\right) = x_2\left(t_i, \mathbf{p}\right), \;\; i = 1, ..., n_{\mathrm{t}}.$$

Assume that there is no input ($u \equiv 0$) and that the initial condition is known to be $\mathbf{x}_0 = (1, 0)^{\mathrm{T}}$.

Differentiating

$$\mathbf{f}\left(\mathbf{x},\mathbf{p},u\right)=\left(\begin{array}{l} -\left(p_1+p_3\right)x_1+p_2x_2+u \\ p1x_1-p_2x_2 \end{array}\right). \tag{11}$$

with respect to each of the parameters in turn, one gets

$$\begin{cases} s_{11}'=-\left(p_1+p_3\right)s_{11}+p_2s_{21}-x_1, \\ s_{21}'=p_1s_{11}-p_2s_{21}+x_1, \\ s_{12}'=-\left(p_1+p_3\right)s_{12}+p_2s_{22}+x_2, \\ s_{22}'=p_1s_{12}-p_2s_{22}-x_2, \\ s_{13}'=-\left(p_1+p_3\right)s_{13}+p_2s_{23}-x_1, \\ s_{23}'=p_1s_{13}-p_2s_{23}. \end{cases} \tag{12}$$

When $\mathbf{x}_0$ independent on $\mathbf{p}$, initial conditions for sensitivity equations are zero.

Coupled system is not cooperative.

Müller's theorem may be helpful.

2.11.3 Reader's Digest Version of Müller's Theorem

Consider the (uncertain) model

$$\dot{\mathbf{x}} = \mathbf{f}\left(\mathbf{x}\left(t\right), \mathbf{p}, t\right), \ \ \mathbf{x}\left(0\right) \in \left[\underline{\mathbf{x}}_0, \overline{\mathbf{x}}_0\right],$$

with $\mathbf{f}\left(\mathbf{x}, \mathbf{p}, t\right)$ continuous on

$$\mathbb{T}: \begin{cases} \boldsymbol{\omega}\left(t\right) \leqslant \mathbf{x} \leqslant \boldsymbol{\Omega}\left(t\right) \\ \underline{\mathbf{p}}_0 \leqslant \mathbf{p} \leqslant \overline{\mathbf{p}}_0 \\ 0 \leqslant t \leqslant T \end{cases}$$

Assume that

1. $\boldsymbol{\omega}(0) = \underline{\mathbf{x}}_0$ and $\boldsymbol{\Omega}(0) = \overline{\mathbf{x}}_0$,

2. $$\left.\begin{array}{l} D^{\pm}\omega_i(t) \leqslant \min_{\underline{\mathbb{T}}_i(t)} f_i(\mathbf{x},\mathbf{p},t), \\ D^{\pm}\Omega_i(t) \geqslant \max_{\overline{\mathbb{T}}_i(t)} f_i(\mathbf{x},\mathbf{p},t), \end{array} , \right\} \text{ for } \; i = 1 \ldots \dim \mathbf{x}$$

   with $\underline{\mathbb{T}}_i(t)$ the subset of $\mathbb{T}$ defined as

   $$\underline{\mathbb{T}}_i(\tau) : \begin{cases} x_i = \omega_i(t), \\ \omega_j(t) \leqslant x_j \leqslant \Omega_j(t), \; j \neq i, \\ \underline{\mathbf{p}}_0 \leqslant \mathbf{p} \leqslant \overline{\mathbf{p}}_0, \\ t = \tau, \end{cases}$$

   and $\overline{\mathbb{T}}_i(t)$ as $\underline{\mathbb{T}}_i(t)$ but with $\omega_i(t)$ replaced by $\Omega_i(t)$.

Then, for any $\mathbf{x}(0) \in [\underline{\mathbf{x}}_0, \overline{\mathbf{x}}_0]$, $\mathbf{p} \in [\underline{\mathbf{p}}_0, \overline{\mathbf{p}}_0]$, and $t \in [0, T]$, a solution exists, such that

$$\boldsymbol{\omega}(t) \leqslant \mathbf{x}(t) \leqslant \boldsymbol{\Omega}(t) .$$

If $\mathbf{f}(\mathbf{x}, \mathbf{p}, t)$ is Lipschitz with respect to $\mathbf{x}$, this solution is the unique one. $\diamondsuit$

$[\boldsymbol{\Phi}](t) = [\boldsymbol{\omega}(t), \boldsymbol{\Omega}(t)]$ is an *inclusion function* for all $\mathbf{x}(\mathbf{p}, t)$.

Building $\boldsymbol{\omega}(t)$ and $\boldsymbol{\Omega}(t)$ is usually easy on a case-by-case basis.

2.11.4 Application of Müller's theorem

Obtaining $\mathbf{x}$, s_{11}, and s_{21} via the simulation of the two 6th-order *deterministic* ODEs

$$\begin{cases} \underline{x}_1' = -(\overline{p}_1 + \overline{p}_3)\underline{x}_1 + \underline{p}_2\underline{x}_2, \\ \underline{x}_2' = \underline{p}_1\underline{x}_1 - \overline{p}_2\underline{x}_2, \\ \overline{x}_1' = -(\underline{p}_1 + \underline{p}_3)\overline{x}_1 + \overline{p}_2\overline{x}_2, \\ \overline{x}_2' = \overline{p}_1\overline{x}_1 - \underline{p}_2\overline{x}_2, \\ \underline{s}_{11}' = -(\overline{p}_1 + \overline{p}_3)\underline{s}_{11} + \underline{p}_2\underline{s}_{21} - \overline{x}_1, \\ \underline{s}_{21}' = \underline{p}_1\underline{s}_{11} - \overline{p}_2\underline{s}_{21} + \underline{x}_1 \end{cases} \tag{13}$$

and

$$\begin{cases} \underline{x}_1' = -(\overline{p}_1 + \overline{p}_3)\underline{x}_1 + \underline{p}_2\underline{x}_2, \\ \underline{x}_2' = \underline{p}_1\underline{x}_1 - \overline{p}_2\underline{x}_2, \\ \overline{x}_1' = -(\underline{p}_1 + \underline{p}_3)\overline{x}_1 + \overline{p}_2\overline{x}_2, \\ \overline{x}_2' = \overline{p}_1\overline{x}_1 - \underline{p}_2\overline{x}_2, \\ \overline{s}_{11}' = -(\underline{p}_1 + \underline{p}_3)\overline{s}_{11} + \overline{p}_2\overline{s}_{21} - \underline{x}_1, \\ \overline{s}_{21}' = \overline{p}_1\overline{s}_{11} - \underline{p}_2\overline{s}_{21} + \overline{x}_1. \end{cases} \tag{14}$$

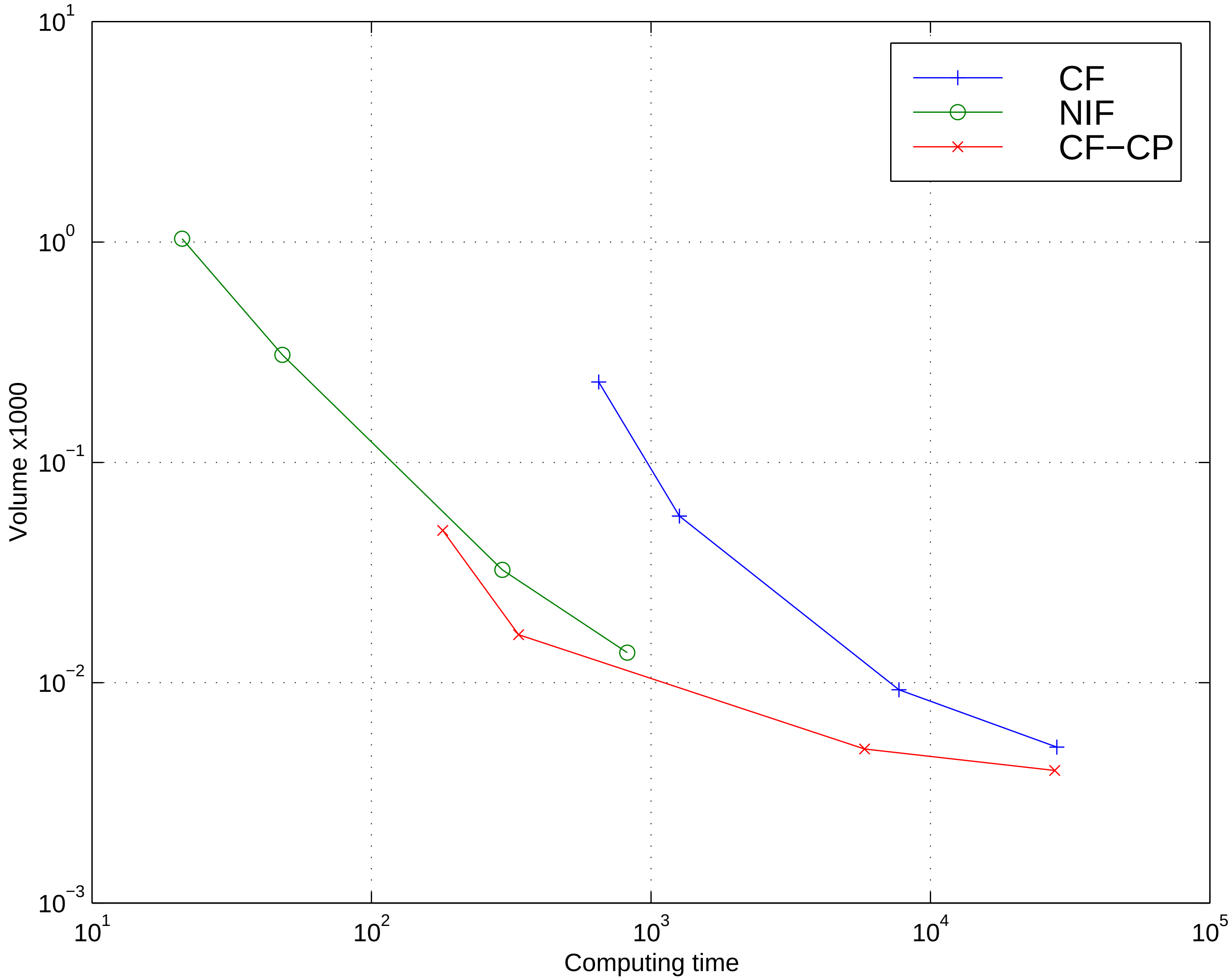
2.11.5 Example - continued

Artificial data generation:

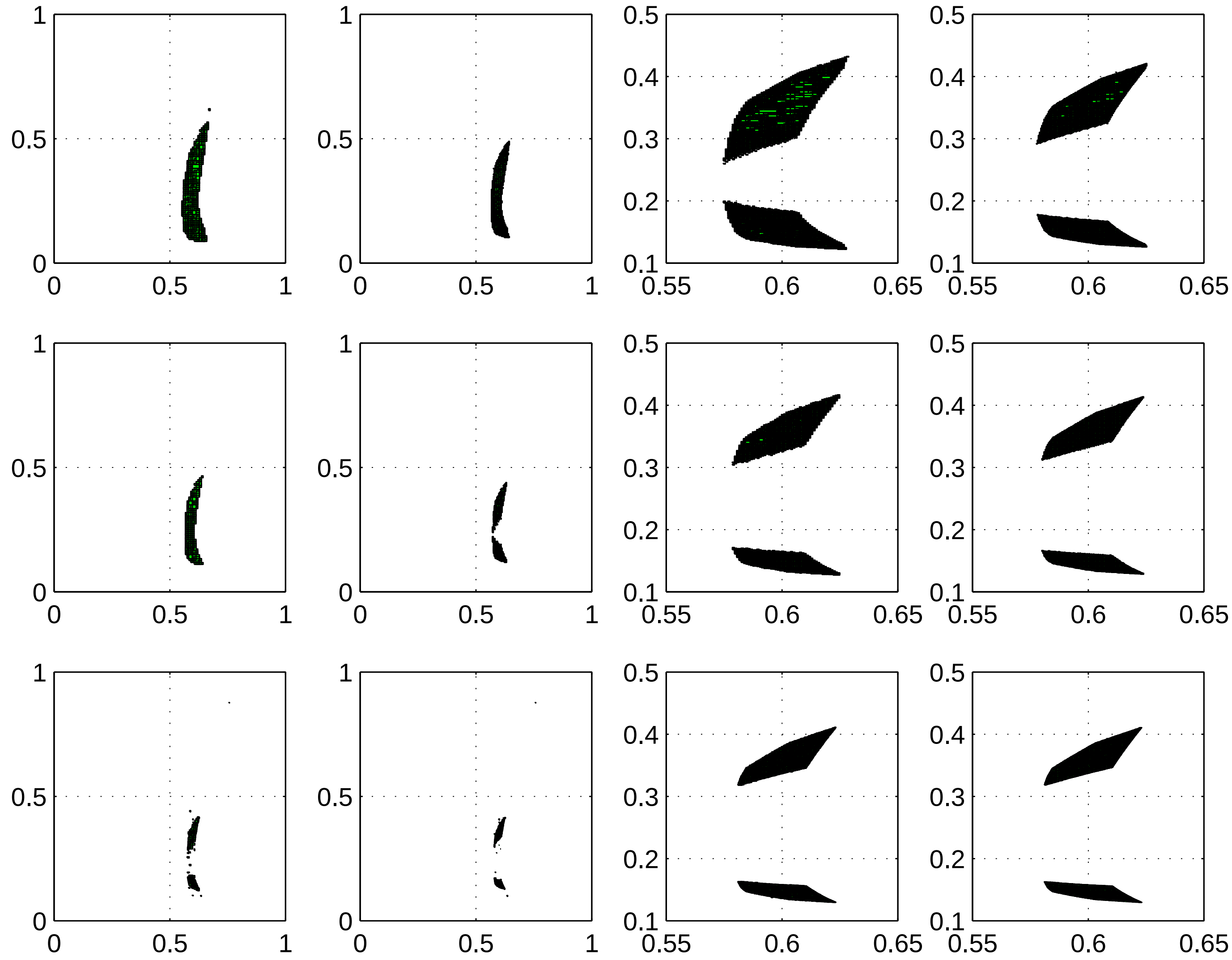
- "true" value of the parameter vector $\mathbf{p}^* = (0.6, 0.15, 0.35)^{\mathrm{T}}$ simulated,
- data obtained by rounding $x_2(t_i)$ to nearest two-digit number for $t_i = i\Delta t$, with $\Delta t = 1$ s and $i = 1, \ldots, 15$,
- initial search domain is $[\mathbf{p}]_0 = [0.01, 1]^{\times 3}$.

Three versions of SIVIA algorithm

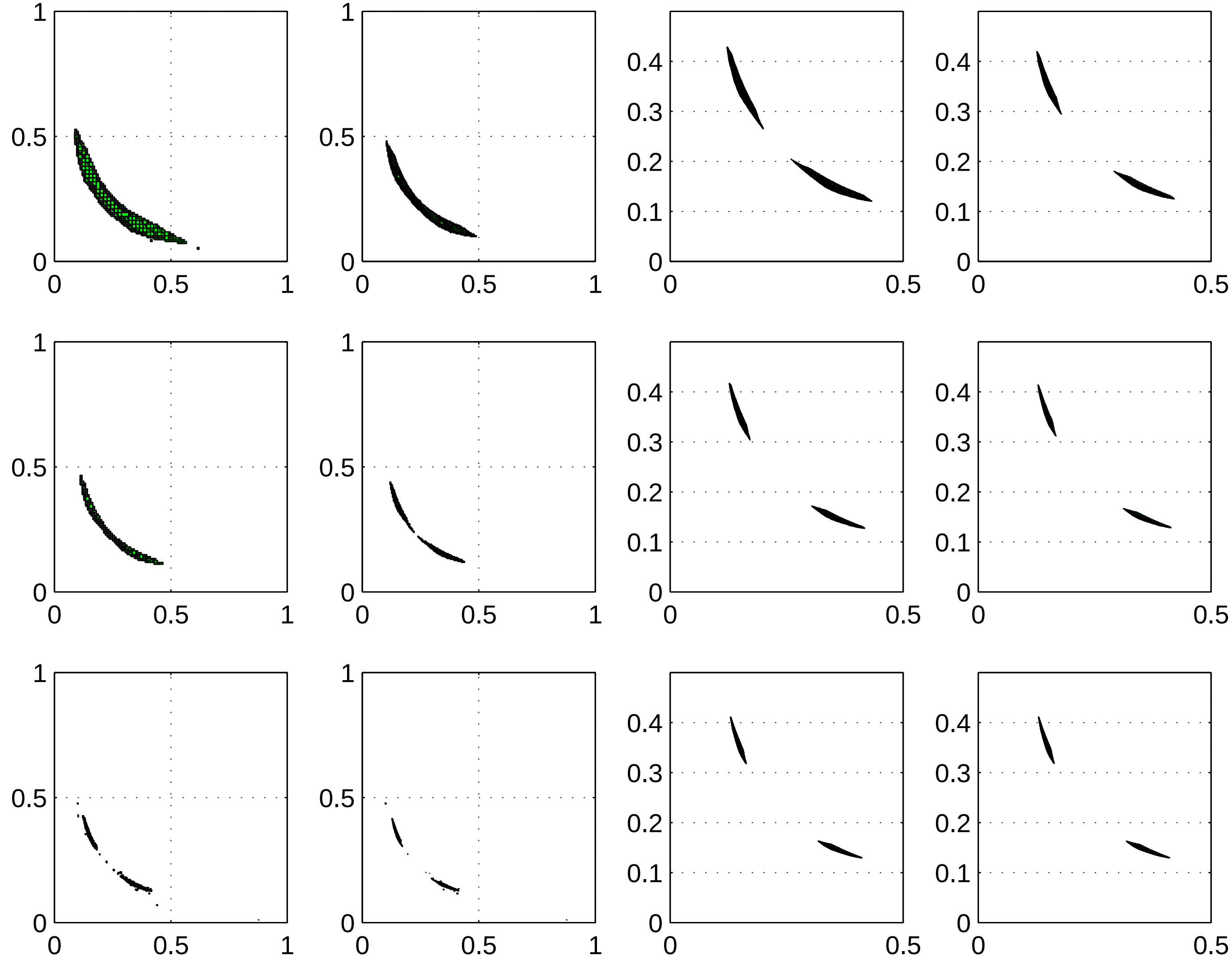
- NIF, the natural inclusion function is used;
- CF uses the centered form,
- CF-CP uses the contractor.



Volume of the solution set as a function of computing time (in seconds)



Projection on the (p_1, p_2)-plane of outer-approximations of the solution set obtained for various values of the precision parameter ε (from left to right, $\varepsilon = 0.01$, $\varepsilon = 0.005$, $\varepsilon = 0.001$, and $\varepsilon = 0.0005$), and for NIF, CF, and CF-CP.



Projection on the (p_2, p_3)-plane of outer-approximations of the solution set obtained for various values of the precision parameter ε (from left to right, $\varepsilon = 0.01$, $\varepsilon = 0.005$, $\varepsilon = 0.001$, and $\varepsilon = 0.0005$), and for NIF, CF, and CF-CP.

Conclusions

- Interval techniques provide guaranteed enclosure of the solution
- ICP or SIVIA + ICP allows more unknown parameters than SIVIA but require an explicit solution for the model
- Alternative approach needs only state equation but still time-consuming
  $\leftarrow$ Guaranteed integration of ODE
  $\leftarrow$ Contractors usable provided that sensitivity fiunctions are employed