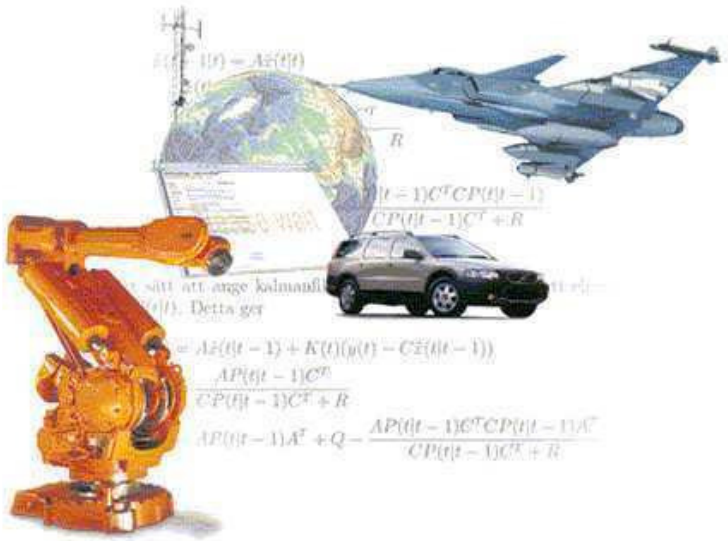
Differential equation models
Interval methods and error analysis



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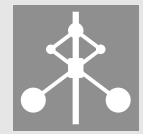
Purpose

- Given a mathematical model with parameters and a set of measurements
- Try to show that
  - either
    no parameter value gives agreement with data
  - or
    there exist some parameters that give agreement with data



A simple model. Two protein reactions

- Protein 1 is changed into Protein 2 with velocity v_1.
- Protein 2 is changed into something else with velocity v_2

$$\dot{x}_1 = -v_1(x_1)$$
$$\dot{x}_2 = -v_2(x_2) + v_1(x_1)$$

x_i protein concentration, v_i reaction velocity

A general model

$$\dot{x} = f(x, \theta), \quad y = h(x), \quad x(0) = x_o$$

- x state vector (typically concentrations)
- θ parameter vector (typically reaction rates)
- y measured variable

The measurements

Suppose there are uncertain output measurements so that it is known that

$$y(t_i) \in I_i = [\ \underline{I_i}, \overline{I_i}], \quad i = 1, \ldots, N$$

or equivalently

$$\underline{I_i} \leq y(t_i) \leq \overline{I_i}, \quad i = 1, \ldots, N$$

The width of the intervals I_i define the measurement uncertainty.

The model rejection problem

- A model is rejected if there is no choice of parameter vector θ for which all $y(t_i)$ lie in the prescribed intervals.
- Usually θ is required to lie in some prescribed set Θ. (For instance reaction rates are positive.)

Approximating the solution

The model is simulated using an algorithm of the form

$$x_{k+1} = x_k + h_k \Phi(x_k, \theta, h_k)$$

(For an Euler method $\Phi = f(x_k, \theta)$)
For every measurement there are usually several time steps so that

$$h_1 + \cdots + h_{N_i - 1} = t_i \tag{1}$$

- Thus x_{N_i} is an approximation of $x(t_i)$.

An interval version of the numeric algorithm

If the parameters lie in a box:

$$\underline{\theta_i} \leq \theta_i \leq \overline{\theta_i}$$

then the equation

$$x_{k+1} = x_k + h_k \Phi(x_k, \theta, h_k)$$

can be used together with interval arithmetic to compute an outer approximation of the solution:

$$\underline{x_k} \leq \theta_k \leq \overline{x_k}$$

The approximation error

The approximation error over a time interval T is

$$||E|| \leq h^p \frac{C'}{L} \left(e^{LT} - 1 \right)$$

- L is the logarithmic norm of f_x
- Ch^{p+1} is the error from one step. C is an expression in the derivatives of f and depends on θ. For most numerical methods (e.g. Runge-Kutta ov various orders) it can be calculated explicitly.

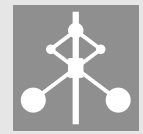
Rejection criterion

Now define the extended intervals

$$I_i^e = [\underline{y_i}, \overline{y_i}] = [\underline{I_i} - C_{N_i}, \overline{I_i} + C_{N_i}]$$

Consider the numerical solution $y_i = h(x_i)$

- If $y_i \notin I_i^e$ then $y(t_i) \notin I_i$.
- Using interval calculations this rejection criterion can be extended to all parameter values in a box.



Acceptance criterion

Similarly one can define contracted intervals

$$I_i^c = [\underline{y_i^c}, \overline{y_i^c}] = [\underline{I_i} + C_{N_i}, \overline{I_i} - C_{N_i}]$$

- If $y_i \in I_i^c$ then $y(t_i) \in I_i$.
- Using interval calculations this acceptance criterion can be extended to all parameters in a box.

A linear example

- Protein 1 is changed into Protein 2 with velocity $\theta_1 x_1$.
- Protein 2 is changed into something else with velocity $\theta_2 x_2$

$$\dot{x}_1 = -\theta_1 x_1$$
$$\dot{x}_2 = -\theta_2 x_2 + \theta_1 x_1$$

In matrix form:

$$\dot{x} = \underbrace{\begin{bmatrix} -\theta_1 & 0 \\ \theta_1 & -\theta_2 \end{bmatrix}}_{A} x$$

Solution

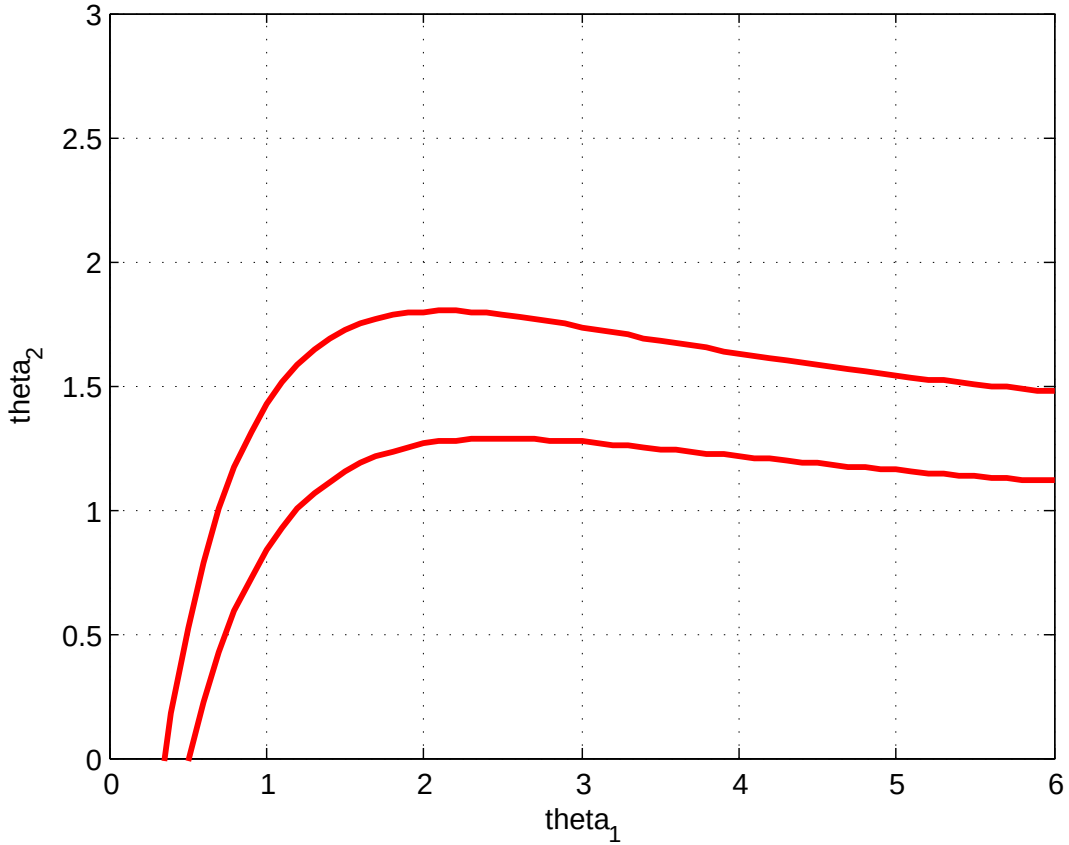
With initial state $x(0) = (1 \ 0)^T$

$$y(t) = x_2(t) = \frac{\theta_1}{\theta_1 - \theta_2} \left(e^{-\theta_2 t} - e^{-\theta_1 t} \right)$$

y is measured.

What do we know from one measurement?

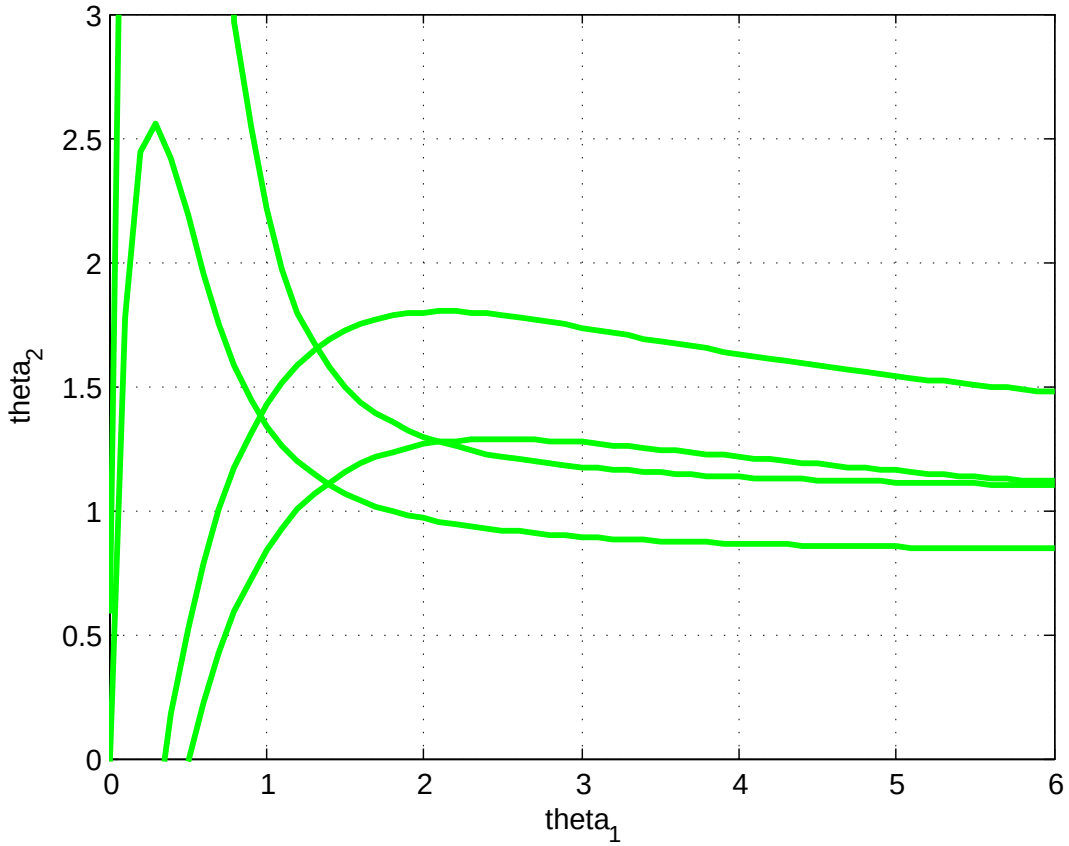
Supposer we know that $0.3 \leq y(1) \leq 0.4$



The parameters are restricted to a strip in θ_1 - θ_2-space.

What do we know from two measurements?

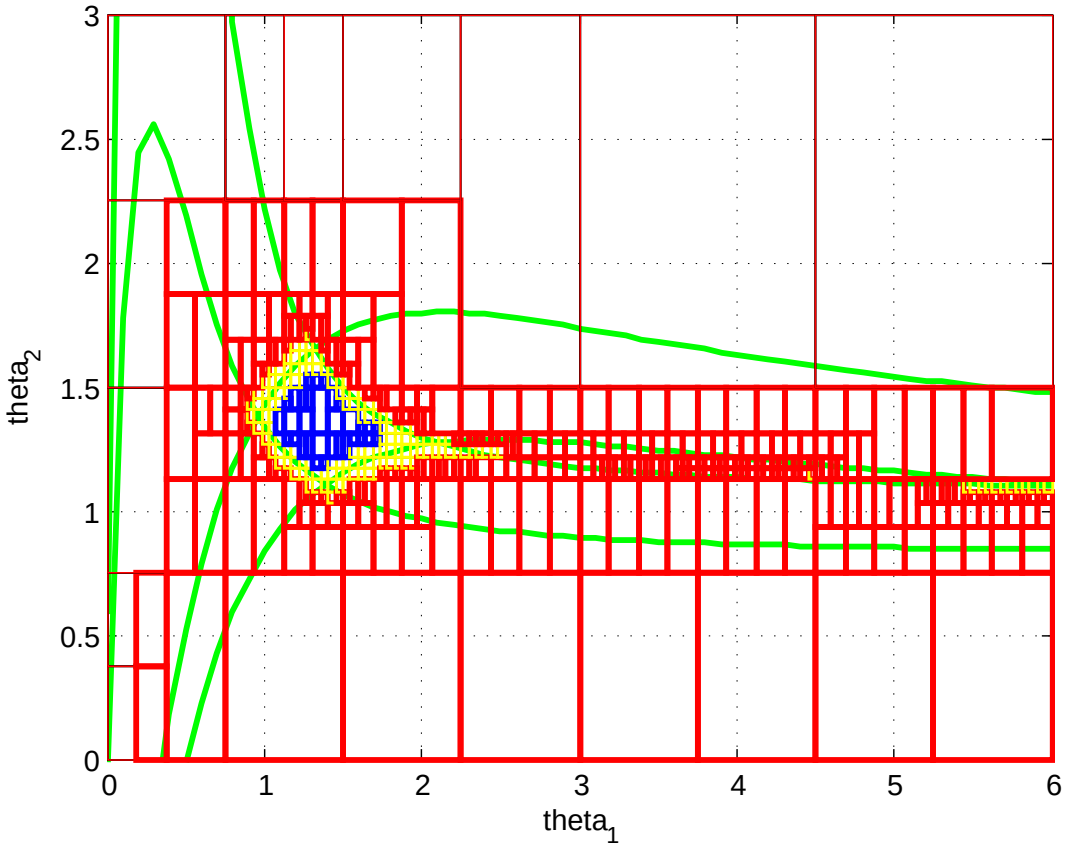
Suppose we know that $0.3 \leq y(1) \leq 0.4$ and $0.015 \leq y(4) \leq 0.04$



Numerical acceptance and rejection

The exact solution can only be calculated in very special cases. Instead one can use the numerical solution and interval calculations to tile the parameter space into boxes in which the model is either rejected or accepted.

The tiled parameter space



red rectangles: rejected

blue rectangles: accepted

yellow rectangles: undecided

Conclusion

Using interval arithmetic together with numerical differential equation solvers it is possible to rigorously accept or reject models at least in simple examples.